Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	1538	(factor adj Xi) or (fxi)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	AND	ON	2005/07/29 18:58
L2	865	l1 and coagul$	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	AND	ON	2005/07/29 18:58
L3	409	l2 and muta$	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	AND	ON	2005/07/29 18:59
L4	1	l3 and (factor adj xi adj muta$)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	AND	ON	2005/07/29 19:01
L5	0	l3 and (fxi adj muta$)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	AND	ON	2005/07/29 19:01

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     (FILE 'HOME' ENTERED AT 10:53:58 ON 29 JUL 2005)

     FILE 'HCAPLUS' ENTERED AT 10:54:04 ON 29 JUL 2005
L1             2 SEA PLU=ON  US 2005143317/PN OR US2003-459910#/AP,PRN
L*** DEL       2 S US 2005143317/PN OR US 2003-459910#/AP,PRN

     FILE 'REGISTRY' ENTERED AT 10:56:17 ON 29 JUL 2005

     FILE 'HCAPLUS' ENTERED AT 10:56:22 ON 29 JUL 2005
L2               TRA L1 1- RN :      229 TERMS

     FILE 'REGISTRY' ENTERED AT 10:56:23 ON 29 JUL 2005
L3           229 SEA PLU=ON  L2
L4            40 SEA PLU=ON  L3 AND FACTOR (1A) XI?
L*** DEL       0 L4 AND S434A
L5            26 SEA PLU=ON  L4 AND 434 (1A) ALAN?
L6            27 SEA PLU=ON  L4 AND 475 (1A) ALAN?
L7            24 SEA PLU=ON  L5 AND L6
L8            20 SEA PLU=ON  L7 AND ((422 OR 437 OR 486 OR 505 OR 509 OR 479 OR
                 476) (1A) ALAN? OR 482 (1A) SER?)
L9            10 SEA PLU=ON  L7 AND 482 (1A) SER?
L10            2 SEA PLU=ON  L7 AND 416 (1A) SER?
                 D SCAN
L11           24 SEA PLU=ON  (L7 OR L8 OR L9 OR L10)

     FILE 'HCAPLUS' ENTERED AT 11:07:12 ON 29 JUL 2005
L12            2 SEA PLU=ON  L11
                 D L12 1-2 IBIB ED
                 E FACTOR XI/CT
L13            0 SEA PLU=ON  BLOOD COAG
L14            0 SEA PLU=ON  BLOOD COAG/CT
                 E BLOOD COAG/CT
                 E ABDEL (1A) MEGUID/AP
                 E ABDEL (1A) MEGUID/IN
                 E ABDEL MEGUID/IN
                 E MEGUID/IN

     FILE 'REGISTRY' ENTERED AT 11:22:46 ON 29 JUL 2005
                 E FACTOR XI/CN

     FILE 'HCAPLUS' ENTERED AT 11:22:46 ON 29 JUL 2005
                 S E4-6

     FILE 'REGISTRY' ENTERED AT 11:23:53 ON 29 JUL 2005
L15            3 SEA PLU=ON  ("FACTOR XI (HUMAN PLASMA SUBUNIT MATURE FORM)"/CN
                 OR "FACTOR XI (HUMAN PLATELET SUBUNIT MATURE FORM)"/CN OR
                 "FACTOR XIA"/CN)

     FILE 'HCAPLUS' ENTERED AT 11:23:54 ON 29 JUL 2005
L16          333 SEA PLU=ON  L15

     FILE 'HCAPLUS' ENTERED AT 11:23:59 ON 29 JUL 2005
L17          333 SEA PLU=ON  L15
L18           42 SEA PLU=ON  L17 AND MUTA?
L19            3 SEA PLU=ON  L18 AND SULF?
L20            3 SEA PLU=ON  L18 AND CRYST?
L21            5 SEA PLU=ON  L18 AND CHARG?
L22           12 SEA PLU=ON  L18 AND TERMIN?
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L23           12 SEA PLU=ON  L18 AND FOLD?
L24           27 SEA PLU=ON  (L19 OR L20 OR L21 OR L22 OR L23)
                 D L24 1-27 IBIB KWIC
                 D COST
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FILE 'STNGUIDE' ENTERED AT 11:33:27 ON 29 JUL 2005

FILE HOME

FILE HCAPLUS

FILE COVERS 1907 - 29 Jul 2005 VOL 143 ISS 6
FILE LAST UPDATED: 28 Jul 2005 (20050728/ED)

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DICTIONARY FILE UPDATES: 28 JUL 2005 HIGHEST RN 857521-63-2

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*******************************************************************
*                                                                 *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added,   *
* effective March 20, 2005.  A new display format, IDERL, is now    *
* available and contains the CA role and document type information. *
*                                                                 *
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Structure search iteration limits have been increased. See HELP SLIMITS for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

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FILE STNGUIDE
FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Jul 22, 2005 (20050722/UP).
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                        data from INPADOC
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 NEWS  9  MAR 22        Original IDE display format returns to REGISTRY/ZREGISTRY
 NEWS 10  MAR 22        PATDPASPC - New patent database available
 NEWS 11  MAR 22        REGISTRY/ZREGISTRY enhanced with experimental property tags
 NEWS 12  APR 04        EPFULL enhanced with additional patent information and new
                        fields
 NEWS 13  APR 04        EMBASE - Database reloaded and enhanced
 NEWS 14  APR 18        New CAS Information Use Policies available online
 NEWS 15  APR 25        Patent searching, including current-awareness alerts (SDIs),
                        based on application date in CA/CAplus and USPATFULL/USPAT2
                        may be affected by a change in filing date for U.S.
                        applications.
 NEWS 16  APR 28        Improved searching of U.S. Patent Classifications for
                        U.S. patent records in CA/CAplus
 NEWS 17  MAY 23        GBFULL enhanced with patent drawing images
 NEWS 18  MAY 23        REGISTRY has been enhanced with source information from
                        CHEMCATS
 NEWS 19  JUN 06        The Analysis Edition of STN Express with Discover!
                        (Version 8.0 for Windows) now available
 NEWS 20  JUN 13        RUSSIAPAT: New full-text patent database on STN
 NEWS 21  JUN 13        FRFULL enhanced with patent drawing images
 NEWS 22  JUN 27        MARPAT displays enhanced with expanded G-group definitions
                        and text labels
 NEWS 23  JUL 01        MEDICONF removed from STN
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=> s us 2005143317/pn or us2003-459910#/ap,prn
             2 US 2005143317/PN
                 (US2005143317/PN)
             0 US2003-459910#/AP
             2 US2003-459910#/PRN
L1           2 US 2005143317/PN OR US2003-459910#/AP,PRN

=> s us 2005143317/pn or us 2003-459910#/ap,prn
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                 (US2005143317/PN)
             0 US 2003-459910#/AP
                 (US2003-459910#/AP)
             2 US 2003-459910#/PRN
                 (US2003-459910#/PRN)
L2           2 US 2005143317/PN OR US 2003-459910#/AP,PRN

=> del l2
DELETE L2? (Y)/N:y

=> d scan

L1     2 ANSWERS    HCAPLUS  COPYRIGHT 2005 ACS on STN
IC     ICM  A61K
CC     7-5 (Enzymes)
       Section cross-reference(s): 1, 63, 75
TI     Crystal structure of coagulation factor XIa-inhibitor complexes yield a
       pharmacophore structure useful for the design of compounds for treatment
       of thrombosis
ST     coagulation factor XIa ligand crystal structure; pharmacophore coagulation
       factor XIa anticoagulant design; conformation coagulation factor XIa
       ligand pharmacophore
IT     Proteins
       RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
          (SBP (sex steroid-binding protein), linker-bound to factor XIa
          inhibitor; crystal structure of coagulation factor XIa-inhibitor
          complexes yield a pharmacophore structure useful for the design of
          compds. for treatment of thrombosis)
IT     Enzyme functional sites
          (active; crystal structure of coagulation factor XIa-inhibitor
          complexes yield a pharmacophore structure useful for the design of
          compds. for treatment of thrombosis)
IT     Heart, disease
          (angina pectoris, unstable, treatment of; crystal structure of
          coagulation factor XIa-inhibitor complexes yield a pharmacophore
          structure useful for the design of compds. for treatment of thrombosis)
IT     Antiarteriosclerotics
          (antiatherosclerotics, treatment of; crystal structure of coagulation
          factor XIa-inhibitor complexes yield a pharmacophore structure useful
          for the design of compds. for treatment of thrombosis)
IT     Artery
          (cerebral, disease, thrombosis, treatment of; crystal structure of
          coagulation factor XIa-inhibitor complexes yield a pharmacophore
          structure useful for the design of compds. for treatment of thrombosis)
IT     Thrombosis
          (coronary arterial, treatment of; crystal structure of coagulation
          factor XIa-inhibitor complexes yield a pharmacophore structure useful
          for the design of compds. for treatment of thrombosis)
IT     Artery
       Vein
          (coronary, thromboembolism, treatment of; crystal structure of
          coagulation factor XIa-inhibitor complexes yield a pharmacophore
          structure useful for the design of compds. for treatment of thrombosis)
IT     Artery, disease
          (coronary, thrombosis, treatment of; crystal structure of coagulation
          factor XIa-inhibitor complexes yield a pharmacophore structure useful
          for the design of compds. for treatment of thrombosis)
IT     Conformation
       Drug design
       Human
       Mus musculus
       Oryctolagus cuniculus
       Peptidomimetics
       Pharmacophores
       Rattus norvegicus
          (crystal structure of coagulation factor XIa-inhibitor complexes yield
          a pharmacophore structure useful for the design of compds. for
          treatment of thrombosis)
IT     Polyoxyalkylenes, biological studies
       RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
          (crystal structure of coagulation factor XIa-inhibitor complexes yield
          a pharmacophore structure useful for the design of compds. for
          treatment of thrombosis)
IT     Artery, disease
       Kidney, disease
       Lung, disease
          (embolism, treatment of; crystal structure of coagulation factor
          XIa-inhibitor complexes yield a pharmacophore structure useful for the
          design of compds. for treatment of thrombosis)
IT     Heart, disease
       Heart, disease
          (infarction, treatment of; crystal structure of coagulation factor
          XIa-inhibitor complexes yield a pharmacophore structure useful for the
          design of compds. for treatment of thrombosis)
IT     Erythrocyte
       Erythrocyte
       Lymphocyte
       Platelet (blood)
          (linker-bound to factor XIa inhibitor; crystal structure of coagulation
          factor XIa-inhibitor complexes yield a pharmacophore structure useful
          for the design of compds. for treatment of thrombosis)
IT     Antibodies and Immunoglobulins
       Ferritins
       Transcortins
       Transferrins
       RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
          (linker-bound to factor XIa inhibitor; crystal structure of coagulation
          factor XIa-inhibitor complexes yield a pharmacophore structure useful
          for the design of compds. for treatment of thrombosis)
IT     Protein sequences
          (of human blood-coagulation factor XIa mutants; crystal structure of
          coagulation factor XIa-inhibitor complexes yield a pharmacophore
          structure useful for the design of compds. for treatment of thrombosis)
IT     Crystal structure
          (of human coagulation factor XIa-inhibitor complexes)
IT     Artery, disease
          (peripheral, occlusion, treatment of; crystal structure of coagulation
          factor XIa-inhibitor complexes yield a pharmacophore structure useful
          for the design of compds. for treatment of thrombosis)
IT     Embolism
          (pulmonary, treatment of; crystal structure of coagulation factor
          XIa-inhibitor complexes yield a pharmacophore structure useful for the
          design of compds. for treatment of thrombosis)
IT     Albumins, biological studies
       RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
          (serum, linker-bound to factor XIa inhibitor; crystal structure of
          coagulation factor XIa-inhibitor complexes yield a pharmacophore
          structure useful for the design of compds. for treatment of thrombosis)
IT     Brain, disease
       Brain, disease
          (stroke, treatment of; crystal structure of coagulation factor
          XIa-inhibitor complexes yield a pharmacophore structure useful for the
          design of compds. for treatment of thrombosis)
IT     Ischemia
          (sudden death, treatment of; crystal structure of coagulation factor
          XIa-inhibitor complexes yield a pharmacophore structure useful for the
          design of compds. for treatment of thrombosis)
IT     Embolism
       Heart
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        (thromboembolism, treatment of; crystal structure of coagulation factor
        XIa-inhibitor complexes yield a pharmacophore structure useful for the
        design of compds. for treatment of thrombosis)
IT   Proteins
     RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
        (thyroxine-binding, linker-bound to factor XIa inhibitor; crystal
        structure of coagulation factor XIa-inhibitor complexes yield a
        pharmacophore structure useful for the design of compds. for treatment
        of thrombosis)
IT   Heart
        (toxicity, thromboembolism, treatment of; crystal structure of
        coagulation factor XIa-inhibitor complexes yield a pharmacophore
        structure useful for the design of compds. for treatment of thrombosis)
IT   Anti-ischemic agents
     Anticoagulants
     Atherosclerosis
        (treatment of; crystal structure of coagulation factor XIa-inhibitor
        complexes yield a pharmacophore structure useful for the design of
        compds. for treatment of thrombosis)
IT   Thrombosis
        (venous, treatment of; crystal structure of coagulation factor
        XIa-inhibitor complexes yield a pharmacophore structure useful for the
        design of compds. for treatment of thrombosis)
IT   Macroglobulins
     RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
        (α2-, linker-bound to factor XIa inhibitor; crystal structure of
        coagulation factor XIa-inhibitor complexes yield a pharmacophore
        structure useful for the design of compds. for treatment of thrombosis)
IT   796962-73-7   796962-74-8   796962-75-9D, ligand complexes   796962-76-0
     796962-77-1   796962-78-2   796962-79-3   796962-80-6   796962-81-7
     796962-82-8D, ligand complexes   796962-83-9   796962-84-0   796962-85-1
     796962-86-2   796962-87-3   800415-12-7D, ligand complexes   800415-13-8D,
     ligand complexes   800415-14-9D, ligand complexes
     RL: BSU (Biological study, unclassified); PRP (Properties); THU
     (Therapeutic use); BIOL (Biological study); USES (Uses)
        (amino acid sequence; crystal structure of coagulation factor
        XIa-inhibitor complexes yield a pharmacophore structure useful for the
        design of compds. for treatment of thrombosis)
IT   618-39-3D, Benzamidine, coagulation factor XI catalytic domain complexes
     9013-55-2D, Blood-coagulation factor XI, ligand complexes   37203-61-5D,
     Blood-coagulation factor XIa, ligand complexes   87928-05-0D, Ecotin,
     coagulation factor XI catalytic domain complexes
     RL: BSU (Biological study, unclassified); PRP (Properties); THU
     (Therapeutic use); BIOL (Biological study); USES (Uses)
        (crystal structure of coagulation factor XIa-inhibitor complexes yield
        a pharmacophore structure useful for the design of compds. for
        treatment of thrombosis)
IT   776305-43-2P   798555-01-8P   798555-02-9P   798555-03-0P   798555-04-1P
     798555-05-2P
     RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU
     (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES
     (Uses)
        (crystal structure of coagulation factor XIa-inhibitor complexes yield
        a pharmacophore structure useful for the design of compds. for
        treatment of thrombosis)
IT   70-11-1, 2-Bromo-1-phenylethanone   100-46-9, Benzyl amine, reactions
     141-90-2, 2-Thiouracil   5292-43-3, tert-Butyl bromoacetate   5538-51-2,
     O-Acetylsalicyloyl chloride   5751-20-2, 2-Methylsulfanyl-3H-pyrimidin-4-
     one   6306-52-1, Valine methyl ester hydrochloride   52927-22-7,
     6-Hydroxynaphthalene-2-carbonitrile   61008-98-8, (R)-m-Chloromandelic
     acid   68635-22-3, 6-Cyano-naphthalene-2-carbonyl chloride   102185-38-6
     132131-24-9, 2-Amino-5-iodobenzonitrile   167678-46-8,
     2-Methyl-3-acetyloxybenzoic chloride   776306-22-0
     RL: RCT (Reactant); RACT (Reactant or reagent)
        (crystal structure of coagulation factor XIa-inhibitor complexes yield
        a pharmacophore structure useful for the design of compds. for
        treatment of thrombosis)
IT   81560-03-4P, 5-Bromo-2-methylsulfanyl-3H-pyrimidin-4-one   142801-55-6P
     201006-25-9P   776305-75-0P   776305-76-1P   776306-08-2P   776306-09-3P
     776306-12-8P, 6-Cyano-2-benzylamidonaphthalene   776306-23-1P
     RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
     (Reactant or reagent)
        (crystal structure of coagulation factor XIa-inhibitor complexes yield
        a pharmacophore structure useful for the design of compds. for
        treatment of thrombosis)
IT   201541-51-7P   294865-55-7P   308276-66-6P   776305-05-6P   776305-06-7P
     776305-07-8P   776305-09-0P   776305-10-3P   776305-11-4P   776305-12-5P
     776305-13-6P   776305-14-7P   776305-15-8P   776305-17-0P   776305-18-1P
     776305-19-2P   776305-20-5P   776305-21-6P   776305-23-8P   776305-24-9P
     776305-25-0P   776305-26-1P   776305-27-2P   776305-28-3P   776305-29-4P
     776305-30-7P   776305-31-8P   776305-32-9P   776305-33-0P   776305-34-1P
     776305-35-2P   776305-36-3P   776305-37-4P   776305-38-5P   776305-39-6P
     776305-40-9P   776305-41-0P   776305-42-1P   776305-44-3P   776305-45-4P
     776305-46-5P   776305-47-6P   776305-48-7P   776305-50-1P   776305-52-3P
     776305-53-4P   776305-54-5P   776305-55-6P   776305-56-7P   776305-57-8P
     776305-58-9P   776305-59-0P   776305-60-3P   776305-61-4P   776305-62-5P
     776305-63-6P   776305-64-7P   776305-66-9P   776305-69-2P   776305-70-5P
     776305-71-6P   776305-73-8P   776305-74-9P   776305-77-2P   776305-78-3P
     776305-80-7P   776305-81-8P   776305-82-9P   776305-84-1P   776305-85-2P
     776305-86-3P   776305-87-4P   776305-89-6P   776305-90-9P   776305-91-0P
     776305-92-1P   776305-93-2P   776305-94-3P   776305-95-4P   776305-96-5P
     776305-98-7P   776305-99-8P   776306-00-4P   776306-01-5P   776306-02-6P
     776306-03-7P   776306-04-8P   776306-06-0P   776306-13-9P   776306-15-1P
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     776306-21-9P   776306-24-2P   776306-25-3P   776306-26-4P   776306-27-5P
     776306-28-6P   776306-30-0P   776306-31-1P   776306-32-2P   776306-33-3P
     776306-34-4P   776306-35-5P   776306-36-6P   776306-37-7P   776306-38-8P
     776306-39-9P   776306-41-3P   776306-43-5P   776306-44-6P   776306-45-7P
     776306-85-5P   798554-83-3P   798554-84-4P   798554-85-5P   798554-86-6P
     798554-87-7P   798554-88-8P   798554-89-9P   798554-90-2P   798554-91-3P
     798554-92-4P   798554-95-7P   798554-96-8P   798554-97-9P   798554-98-0P
     798554-99-1P   798555-00-7P
     RL: SPN (Synthetic preparation); PREP (Preparation)
        (crystal structure of coagulation factor XIa-inhibitor complexes yield
        a pharmacophore structure useful for the design of compds. for
        treatment of thrombosis)
IT   25322-68-3, Polyethylene glycol
     RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
        (linker for attachment to blood component; crystal structure of
        coagulation factor XIa-inhibitor complexes yield a pharmacophore
        structure useful for the design of compds. for treatment of thrombosis)
IT   800415-15-0D, ligand complexes
     RL: BSU (Biological study, unclassified); PRP (Properties); BIOL
     (Biological study)
        (nucleotide sequence; crystal structure of coagulation factor
        XIa-inhibitor complexes yield a pharmacophore structure useful for the
        design of compds. for treatment of thrombosis)
IT   800924-46-3   800924-47-4   800924-48-5   800924-49-6
     RL: PRP (Properties)
        (unclaimed nucleotide sequence; crystal structure of coagulation factor
        XIa-inhibitor complexes yield a pharmacophore structure useful for the
        design of compds. for treatment of thrombosis)

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http://www.cas.org/ONLINE/DBSS/registryss.html

=> tra rn
L2          TRANSFER L1 1- RN :       229 TERMS
L3           229 L2

=> l3 and factor (1a) xi?
        113963 FACTOR
           570 FACTORS
        114379 FACTOR
                 (FACTOR OR FACTORS)
         26586 XI?
           811 FACTOR (1A) XI?
L4          40 L3 AND FACTOR (1A) XI?

=> d scan

L4   40 ANSWERS   REGISTRY  COPYRIGHT 2005 ACS on STN
IN   Blood-coagulation factor XI, pro- (human) (9CI)
SQL  625
MF   Unspecified
CI   MAN

**RELATED SEQUENCES AVAILABLE WITH SEQLINK**

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):0

=> l4 and s434a
             0 S434A
L5           0 L4 AND S434A

=> d scan l4

L4   40 ANSWERS   REGISTRY  COPYRIGHT 2005 ACS on STN
IN   Blood-coagulation factor XI [434-alanine,475-alanine,482-alanine]
     (human) (9CI)
SQL  607
MF   Unspecified
CI   MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):0

=> del l5
DELETE L5? (Y)/N:y

=> l4 and 434 (1a) alan?
          4976 434
       1008919 ALAN?
            52 434 (1A) ALAN?
L5          26 L4 AND 434 (1A) ALAN?

=> l4 and 475 (1a) alan?
          4599 475
       1008919 ALAN?
            28 475 (1A) ALAN?
L6          27 L4 AND 475 (1A) ALAN?

=> l5 and l6
L7          24 L5 AND L6

=> l7 and ((422 or 437 or 486 or 505 or 509 or 479 or 476) (1a) alan? or 482 (1a)
ser?)
          4798 422
          4765 437
          4536 486
          4709 505
          4375 509
          4283 479
          4450 476
       1008919 ALAN?
            98 (422 OR 437 OR 486 OR 505 OR 509 OR 479 OR 476) (1A) ALAN?
          4563 482
        605713 SER?
            16 482 (1A) SER?
L8          20 L7 AND ((422 OR 437 OR 486 OR 505 OR 509 OR 479 OR 476) (1A)
```

```
              ALAN? OR 482 (1A) SER?)

=> l7 and 482 (1a) ser?
          4563 482
        605713 SER?
            16 482 (1A) SER?
L9          10 L7 AND 482 (1A) SER?

=> d scan

L9   10 ANSWERS   REGISTRY  COPYRIGHT 2005 ACS on STN
IN   370-607-Blood-coagulation factor XI [434-alanine,475-alanine,482-
     serine] (human) (9CI)
SQL  238
MF   Unspecified
CI   MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):
HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):1

L9   10 ANSWERS   REGISTRY  COPYRIGHT 2005 ACS on STN
IN   Blood-coagulation factor XI [416-serine,434-alanine,475-alanine,482-
     serine] (human) (9CI)
SQL  607
MF   Unspecified
CI   MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):0

=> l7 and 416 (1a) ser?
          4866 416
        605713 SER?
             5 416 (1A) SER?
L10          2 L7 AND 416 (1A) SER?

=> d scan

L10  2 ANSWERS   REGISTRY  COPYRIGHT 2005 ACS on STN
IN   Blood-coagulation factor XI [416-serine,434-alanine,475-alanine,482-
     serine] (human) (9CI)
SQL  607
MF   Unspecified
CI   MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):1

L10  2 ANSWERS   REGISTRY  COPYRIGHT 2005 ACS on STN
IN   370-607-Blood-coagulation factor XI [416-serine,434-alanine,475-
     alanine,482-serine] (human) (9CI)
SQL  238
MF   Unspecified
```

```
CI   MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***

ALL ANSWERS HAVE BEEN SCANNED

=> d his

     (FILE 'HOME' ENTERED AT 10:53:58 ON 29 JUL 2005)

     FILE 'HCAPLUS' ENTERED AT 10:54:04 ON 29 JUL 2005
L1            2 S US 2005143317/PN OR US2003-459910#/AP,PRN

     FILE 'REGISTRY' ENTERED AT 10:56:17 ON 29 JUL 2005

     FILE 'HCAPLUS' ENTERED AT 10:56:22 ON 29 JUL 2005
L2              TRA L1 1- RN :      229 TERMS

     FILE 'REGISTRY' ENTERED AT 10:56:23 ON 29 JUL 2005
L3          229 SEA L2
L4           40 L3 AND FACTOR (1A) XI?
L5           26 L4 AND 434 (1A) ALAN?
L6           27 L4 AND 475 (1A) ALAN?
L7           24 L5 AND L6
L8           20 L7 AND ((422 OR 437 OR 486 OR 505 OR 509 OR 479 OR 476) (1A) AL
L9           10 L7 AND 482 (1A) SER?
L10           2 L7 AND 416 (1A) SER?

=> s l7-10
L11          24 (L7 OR L8 OR L9 OR L10)

=> fil hcap
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FILE LAST UPDATED: 28 Jul 2005  (20050728/ED)

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 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> s l11
L12           2 L11
```

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=> d l12 1-2 ibib ed

L12  ANSWER 1 OF 2  HCAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2004:1033547  HCAPLUS Full-text
DOCUMENT NUMBER:          142:19250
TITLE:                    Crystal structure of coagulation factor XIa-inhibitor
                          complexes yield a pharmacophore structure useful for
                          the design of compounds for treatment of thrombosis
INVENTOR(S):              Abdel-Meguid, Sherin S.; Babine, Robert E.; Deng,
                          Hongfeng; Jin, Lei; Lin, Jian; Magee, Scott R.;
                          Meyers, Harold V.; Pandey, Pramod; Rynkiewicz, Michael
                          J.; Weaver, David T.
PATENT ASSIGNEE(S):       Suntory Pharmaceutical Research Laboratories Llc, USA
SOURCE:                   PCT Int. Appl., 925 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   2
PATENT INFORMATION:

     PATENT NO.          KIND   DATE        APPLICATION NO.         DATE
     ---------------     ----   --------    --------------------    --------
     WO 2004103270        A2    20041202    WO 2004-US10349         20040402
     WO 2004103270        A3    20050512
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
             LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
             NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
             TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ,
             BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE,
             ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI,
             SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN,
             TD, TG
     US 2005143317        A1    20050630    US 2004-817248          20040402
PRIORITY APPLN. INFO.:                      US 2003-459910P     P   20030402
OTHER SOURCE(S):          MARPAT 142:19250
ED   Entered STN:  02 Dec 2004

L12  ANSWER 2 OF 2  HCAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2004:878270  HCAPLUS Full-text
DOCUMENT NUMBER:          141:360682
TITLE:                    Blood coagulation factor XI inhibitors and methods for
                          treatment of thrombosis
INVENTOR(S):              Abdel-Meguid, Sherin S.; Babine, Robert E.; Deng,
                          Hongfeng; Jin, Lei; Lin, Jian; Magee, Scott R.;
                          Meyers, Harold V.; Pandey, Pramod; Rynkiewicz, Michael
                          J.; Weaver, David T.
PATENT ASSIGNEE(S):       Suntory Pharmaceutical Research Laboratories, LLC, USA
SOURCE:                   PCT Int. Appl., 251 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   2
PATENT INFORMATION:

     PATENT NO.          KIND   DATE        APPLICATION NO.         DATE
     ---------------     ----   --------    --------------------    --------
```

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     WO 2004089297        A2    20041021    WO 2004-US10300         20040402
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
             LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
             NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
             TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ,
             BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE,
             ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI,
             SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN,
             TD, TG
     US 2005143317        A1    20050630    US 2004-817248          20040402
PRIORITY APPLN. INFO.:                      US 2003-459910P     P   20030402
OTHER SOURCE(S):          MARPAT 141:360682
ED   Entered STN:  22 Oct 2004


=> e factor xi/ct
E#   FREQUENCY    AT     TERM
--   ---------    --     ----
E1           0     2     FACTOR X/CT
E2           0     2     FACTOR XA/CT
E3           0       --> FACTOR XI/CT
E4           0     2     FACTOR XIII/CT
E5           0     2     FACTOR XIIIA/CT
E6           0     1     FACTOR-A/CT
E7           0     1     FACTOR-A-CONVERTING/CT
E8           0     1     FACTOR-B/CT
E9           0     1     FACTOR-B-INDUCIBLE/CT
E10          0     1     FACTOR-B1/CT
E11          0     1     FACTOR-KB/CT
E12          0     1     FACTOR-1/CT

=> s blood coag
       1196838 BLOOD
          1197 BLOODS
       1196966 BLOOD
                 (BLOOD OR BLOODS)
            98 COAG
L13          0 BLOOD COAG
                 (BLOOD(W)COAG)

=> s blood coag/ct
L14          0 BLOOD COAG/CT

=> e blood coag/ct
E#   FREQUENCY    AT     TERM
--   ---------    --     ----
E1           0     2     BLOOD CLOTTING FACTOR S/CT
E2           0     2     BLOOD CLOTTING FACTORS/CT
E3           0       --> BLOOD COAG/CT
E4       20139    26     BLOOD COAGULATION/CT
E5           0    20     BLOOD COAGULATION (L) DISORDER/CT
E6           0     2     BLOOD COAGULATION (L) DISORDER, DISSEMINATED INTRAVASC
                         ULAR/CT
E7           0    11     BLOOD COAGULATION (L) DISORDER, HEMORRHAGIC DIATHESIS/
                         CT
E8           0     2     BLOOD COAGULATION (L) DISORDER, HERMANSKY-PUDLAK SYNDR
```

```
                             OME/CT
E9           0       2       BLOOD COAGULATION (L) DISORDER, HYPERCOAGULABILITY/CT
E10          0      13       BLOOD COAGULATION (L) DISSEMINATED INTRAVASCULAR/CT
E11          0      10       BLOOD COAGULATION (L) EXTRINSIC/CT
E12          0       2       BLOOD COAGULATION (L) HEMORRHAGIC DIATHESIS/CT

=> e
E13          0      10       BLOOD COAGULATION (L) HERMANSKY-PUDLAK SYNDROME/CT
E14          0      14       BLOOD COAGULATION (L) HYPERCOAGULABILITY/CT
E15          0       9       BLOOD COAGULATION (L) INTRINSIC/CT
E16          0       2       BLOOD COAGULATION DISORDERS/CT
E17          0       2       BLOOD COAGULATION FACTOR S/CT
E18          1               BLOOD COAGULATION FACTORS/CT
E19          0       2       BLOOD COAGULATION-INHIBITING RODENTICIDES/CT
E20          0       2       BLOOD COAGULATORS/CT
E21          0       2       BLOOD CONTAINERS/CT
E22       1565       2       BLOOD CORPUSCLE/CT
E23          0       2       BLOOD CORPUSCLE (L) DENDRITIC CELL/CT
E24          0       3       BLOOD CORPUSCLE (L) DISEASE, CYTOPENIA/CT

=>

=> d his

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     FILE 'HCAPLUS' ENTERED AT 10:54:04 ON 29 JUL 2005
L1            2 S US 2005143317/PN OR US2003-459910#/AP,PRN

     FILE 'REGISTRY' ENTERED AT 10:56:17 ON 29 JUL 2005

     FILE 'HCAPLUS' ENTERED AT 10:56:22 ON 29 JUL 2005
L2              TRA L1 1- RN :       229 TERMS

     FILE 'REGISTRY' ENTERED AT 10:56:23 ON 29 JUL 2005
L3          229 SEA L2
L4           40 L3 AND FACTOR (1A) XI?
L5           26 L4 AND 434 (1A) ALAN?
L6           27 L4 AND 475 (1A) ALAN?
L7           24 L5 AND L6
L8           20 L7 AND ((422 OR 437 OR 486 OR 505 OR 509 OR 479 OR 476) (1A) AL
L9           10 L7 AND 482 (1A) SER?
L10           2 L7 AND 416 (1A) SER?
L11          24 S L7-10

     FILE 'HCAPLUS' ENTERED AT 11:07:12 ON 29 JUL 2005
L12           2 S L11
                E FACTOR XI/CT
L13           0 S BLOOD COAG
L14           0 S BLOOD COAG/CT
                E BLOOD COAG/CT

=> e abdel (1a) meguid/ap
**** START OF FIELD ****
E3            0 --> ABDEL (1A) MEGUID/AP
E4            1     AP2000-1754/AP
E5            1     AP2000-200001732/AP
E6            1     AP2000-200001739/AP
E7            1     AP2000-200001741/AP
E8            1     AP2000-200001751/AP
E9            1     AP2000-200001767/AP
E10           1     AP2000-200001768/AP
E11           1     AP2000-200001771/AP
E12           1     AP2000-200001780/AP

=> e abdel (1a) meguid/in
E1            1     ABDEEV RAFAIL A/IN
E2            5     ABDEEV YU M/IN
E3            0 --> ABDEL (1A) MEGUID/IN
E4            1     ABDEL AAL EL SAYED A/IN
E5            1     ABDEL ALAFANDI HAMID/IN
E6            2     ABDEL BAKY SAMY/IN
E7            1     ABDEL BARY ELSAYED MOHAMED/IN
E8            1     ABDEL BARY MAMDOUH/IN
E9            1     ABDEL BASET MAHMOUD BADR/IN
E10           1     ABDEL FATTAH SABRY HOSEIN KAMEL/IN
E11           1     ABDEL FATTAH TAREK M/IN
E12           1     ABDEL GADIR WARDA SHUKART ALLAH/IN

=> e abdel meguid/in
E1            3     ABDEL MALIK MAGDY M/IN
E2            4     ABDEL MALIK MAGDY MALAK/IN
E3            0 --> ABDEL MEGUID/IN
E4            1     ABDEL MEGUID SHERIN/IN
E5            7     ABDEL MEGUID SHERIN S/IN
E6            2     ABDEL MEGUID SHERIN SALAHELDIN/IN
E7            1     ABDEL MEQUID SHERIN SALAHELDIN/IN
E8            1     ABDEL MONEM AHMED/IN
E9            1     ABDEL MONEM MAHAMOUD M/IN
E10           1     ABDEL MONEM MAHMOND M/IN
E11          18     ABDEL MONEM MAHMOUD M/IN
E12           1     ABDEL NABI SUMRO/IN

=> e meguid/in
E1            1     MEGUIAR FLOYD/IN
E2            1     MEGUIAR FLOYD L/IN
E3            0 --> MEGUID/IN
E4            1     MEGUID MICHAEL M/IN
E5            1     MEGUMI HIROSHI/IN
E6            2     MEGUMI HIROTOSHI/IN
E7            1     MEGUMI ITO NORMA/IN
E8            7     MEGUMI KOICHI/IN
E9            1     MEGUMI KOUITI/IN
E10           1     MEGUMI MICHIO/IN
E11           1     MEGUMI NAOMITSU/IN
E12           1     MEGUMI SAITO/IN

=> e factor XI/cn
   REGIstRY INITIATED
Substance data EXPAND from CAS REGISTRY in progress...


E1            1     FACTOR XA-1/CN
E2            1     FACTOR XA-DIRECTED ANTICOAGULANT (YELLOW FEVER MOSQUITO CLON
                    E 8-2B GENE AFXA PRECURSOR REDUCED)/CN
E3            0 --> FACTOR XI/CN
E4            1     FACTOR XI (HUMAN PLASMA SUBUNIT MATURE FORM)/CN
E5            1     FACTOR XI (HUMAN PLATELET SUBUNIT MATURE FORM)/CN
E6            1     FACTOR XIA/CN
E7            1     FACTOR XII (HUMAN FACTOR XII GENE F12 FRAMESHIFT MUTATION C-
                    TERMINAL FRAGMENT)/CN
E8            1     FACTOR XII (HUMAN MUTANT GENE EXON 12 MUTATION 55 C-TERMINAL
                    FRAGMENT)/CN
E9            1     FACTOR XIIA/CN
E10           1     FACTOR XIII/CN
E11           1     FACTOR Y (STREPTOCOCCUS PNEUMONIAE STRAIN R6 GENE PRIA)/CN
E12           1     FACTOR-FOR-INVERSION STIMULATION PROTEIN (BUCHNERA APHIDICOL
                    A STRAIN SG GENE FIS)/CN

=> s e4-6
   REGIstRY INITIATED
Substance data SEARCH and crossover from CAS REGISTRY in progress...
Use DISPLAY HITSTR (or FHITSTR) to directly view retrieved structures.



L16         333 L15

=> fil hcap
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FILE LAST UPDATED: 28 Jul 2005  (20050728/ED)

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 substance identification.

=> l16
L17         333 L15

=> l17 and muta?
        495859 MUTA?
L18            42 L17 AND MUTA?

=> l18 and sulf?
       1648834 SULF?
L19             3 L18 AND SULF?

=> l18 and cryst?
       1960607 CRYST?
L20             3 L18 AND CRYST?

=> l18 and charg?
        685452 CHARG?
L21             5 L18 AND CHARG?

=> l18 and termin?
        528687 TERMIN?
L22            12 L18 AND TERMIN?

=> l18 and fold?
        482293 FOLD?
L23            12 L18 AND FOLD?

=> l19-23
L24            27 (L19 OR L20 OR L21 OR L22 OR L23)

=> d scan

L24   27 ANSWERS   HCAPLUS  COPYRIGHT 2005 ACS on STN
CC    7-3 (Enzymes)
      Section cross-reference(s): 14
TI    Alpha-1-antitrypsin-Pittsburgh. A potent inhibitor of human plasma factor
      XIa, kallikrein, and factor XIIf
ST    antitrypsin alpha1 Pittsburgh plasma proteolysis; kallikrein inhibition
      alpha1 antitrypsin Pittsburgh; factor XIa XIIf alpha1 antitrypsin
      Pittsburgh
IT    Kinetics, enzymic
         (of inactivation, of kallikrein and blood-coagulation factors XIa and
         XIIf of human, mutation in α1-antitrypsin in relation
         to)
IT    9041-92-3
      RL: BIOL (Biological study)
         (Pittsburgh, kallikrein and blood-coagulation factors XIa and XIIf of
         human inhibition by, kinetics of)
IT    9001-01-8  37203-61-5   75216-42-1
      RL: PROC (Process)
         (inhibition of, by α1-antitrypsin-Pittsburgh of human, kinetics
         of)
IT    9002-04-4
      RL: BIOL (Biological study)
         (α1-antitrypsin-Pittsburgh of human inhibition of, kinetics of)

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):1

L24   27 ANSWERS   HCAPLUS  COPYRIGHT 2005 ACS on STN
CC    7-3 (Enzymes)
TI    Domain V of β2-Glycoprotein I Binds Factor XI/XIa and Is Cleaved at
      Lys317-Thr318
ST    domain V beta2 glycoprotein I binding factor XI XIa
IT    Apolipoproteins
      RL: BSU (Biological study, unclassified); BIOL (Biological study)
         (H; domain V of β2-glycoprotein I binds factor XI/XIa and is
         cleaved at Lys317-Thr318)
IT    Fibrinolysis
      Thrombus
         (cleavage of β2-glycoprotein I may represent unique mechanism in
         control of factor XI/XIa activation and fibrinolysis)
```

IT Protein motifs
(domain V; domain V of β2-glycoprotein I binds factor XI/XIa and is cleaved at Lys317-Thr318)
IT Molecular association
(β2-glycoprotein I-factor XI/XIa; Lys284, Lys286, and Lys287 residues in domain V of β2-glycoprotein I play important role in factor XI/XIa binding)
IT 56-87-1, L-Lysine, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Lys284, Lys286, and Lys287 residues in domain V of β2-glycoprotein I play important role in factor XI/XIa binding)
IT 9013-55-2, Blood-coagulation factor XI 37203-61-5, Blood-coagulation factor XIa
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(domain V of β2-glycoprotein I binds factor XI/XIa and is cleaved at Lys317-Thr318)

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):1

L24 27 ANSWERS HCAPLUS COPYRIGHT 2005 ACS on STN
CC 14-6 (Mammalian Pathological Biochemistry)
Section cross-reference(s): 3, 7
TI Severe factor XI deficiency caused by a Gly555 to Glu mutation (factor XI-Glu555): a cross-reactive material positive variant defective in factor IX activation
ST factor IX activation blood coagulation factor IX deficiency
IT Blood coagulation
(disorder; severe factor XI deficiency caused by Gly555 to Glu mutation (factor XI-Glu555) in relation to factor IX activation)
IT Gene, animal
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(factor XI; severe factor XI deficiency caused by Gly555 to Glu mutation (factor XI-Glu555) in relation to factor IX activation)
IT Gene, animal
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(factor XIa; severe factor XI deficiency caused by Gly555 to Glu mutation (factor XI-Glu555) in relation to factor IX activation)
IT Blood plasma
Human
Molecular association
Mutation
Thrombus
(severe factor XI deficiency caused by Gly555 to Glu mutation (factor XI-Glu555) in relation to factor IX activation)
IT 56-40-6, Glycine, biological studies 9000-94-6, Antithrombin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(severe factor XI deficiency caused by Gly555 to Glu mutation (factor XI-Glu555) in relation to factor IX activation)
IT 9001-28-9, Factor IX 9013-55-2, Blood-coagulation factor XI 37203-61-5, Factor XIa 37316-87-3, Factor IXa
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(severe factor XI deficiency caused by Gly555 to Glu mutation (factor XI-Glu555) in relation to factor IX activation)

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):1

L24 27 ANSWERS HCAPLUS COPYRIGHT 2005 ACS on STN
CC 1-12 (Pharmacology)
Section cross-reference(s): 6
TI Expression, purification, biochemical and pharmacological characterization of a recombinant aprotinin variant
ST aprotinin variant serine protease inhibitor
IT Edema
Hemorrhage
(cerebral; expression, purification, biochem. and pharmacol. characterization of recombinant aprotinin variant)
IT Brain, disease
(edema; expression, purification, biochem. and pharmacol. characterization of recombinant aprotinin variant)
IT Circulation
Hemostatics
Human
(expression, purification, biochem. and pharmacol. characterization of recombinant aprotinin variant)
IT Brain, disease
(hemorrhage; expression, purification, biochem. and pharmacol. characterization of recombinant aprotinin variant)
IT 9000-81-1, Acetylcholinesterase 9001-01-8, Urinary kallikrein 9001-90-5, Plasmin 9002-04-4, Thrombin 9002-05-5, Factor Xa 9002-07-7, Trypsin 9004-07-3, Chymotrypsin 9039-53-6, Urokinase 37203-61-5, Factor XIa 42617-41-4, Protein Ca 56645-49-9, Cathepsin G 80295-34-7, Complement C1r 80295-35-8, Complement C1s 97501-93-4, Tryptase 105857-23-6, TPA 111691-85-1, Blood-coagulation factor XIIaβ (human light chain) 410538-33-9, Plasmakallikrein
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(expression, purification, biochem. and pharmacol. characterization of recombinant aprotinin variant)
IT 9087-70-1, Aprotinin
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(expression, purification, biochem. and pharmacol. characterization of recombinant aprotinin variant)
IT 807370-94-1P
RL: PAC (Pharmacological activity); PNU (Preparation, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(expression, purification, biochem. and pharmacol. characterization of recombinant aprotinin variant)
IT 9004-06-2, Elastase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(of leukocytes; expression, purification, biochem. and pharmacol. characterization of recombinant aprotinin variant)

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):0

=> d l24 1-27 ibib kwic

L24 ANSWER 1 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:108543 HCAPLUS Full-text
DOCUMENT NUMBER: 142:331817
TITLE: Crystal Structures of the FXIa Catalytic Domain in Complex with Ecotin Mutants Reveal Substrate-like Interactions
AUTHOR(S): Jin, Lei; Pandey, Pramod; Babine, Robert E.; Gorga, Joan C.; Seidl, Katherine J.; Gelfand, Ellen; Weaver, David T.; Abdel-Meguid, Sherin S.; Strickler, James E.
CORPORATE SOURCE: Daiichi Asubio Medical Research Laboratories LLC, Cambridge, MA, 02139, USA
SOURCE: Journal of Biological Chemistry (2005), 280(6), 4704-4712
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
TI Crystal Structures of the FXIa Catalytic Domain in Complex with Ecotin Mutants Reveal Substrate-like Interactions
AB Thrombosis can lead to life-threatening conditions such as acute myocardial infarction, pulmonary embolism, and stroke. Although commonly used anti-coagulant drugs, such as low mol. weight heparin and warfarin, are effective, they carry a significant risk of inducing severe bleeding complications, and there is a need for safer drugs. Activated Factor XI (FXIa) is a key enzyme in the amplification phase of the coagulation cascade. Anti-human FXI antibody significantly reduces thrombus growth in a baboon thrombosis model without bleeding problems. Therefore, FXIa is a potential target for anti-thrombosis therapy. To determine the structure of FXIa, we derived a recombinant catalytic domain of FXI, consisting of residues 370-607 (rhFXI370-607). Here we report the first crystal structure of rhFXI370-607 in complex with a substitution mutant of ecotin, a panserine protease protein inhibitor secreted by Escherichia coli, to 2.2 Å resolution. The presence of ecotin not only assisted in the crystallization of the enzyme but also revealed unique structural features in the active site of FXIa. Subsequently, the sequence from P5 to P2' in ecotin was mutated to the FXIa substrate sequence, and the structures of the rhFXI370-607-ecotin mutant complexes were determined. These structures provide us with an understanding of substrate binding interactions of FXIa, the structural information essential for the structure-based design of FXIa-selective inhibitors.
ST crystal structure coagulation factor XIa human ecotin drug design
IT Enzyme functional sites
(active; atomic resolution crystallog. structures of blood coagulation factor XIa catalytic domain in complex with ecotin mutants)
IT Anticoagulants
Blood coagulation
Drug design
Human
Molecular recognition
(atomic resolution crystallog. structures of blood coagulation factor XIa catalytic domain in complex with ecotin mutants)
IT Enzyme functional sites
(inhibitor-binding, heparin-binding; atomic resolution crystallog. structures of blood coagulation factor XIa catalytic domain in complex with ecotin mutants)
IT Crystal structure
(of blood coagulation factor XIa catalytic domain in complex with ecotin mutants)
IT Conformation
Quaternary structure
(protein; atomic resolution crystallog. structures of blood coagulation factor XIa catalytic domain in complex with ecotin mutants)
IT 37203-61-5DP, Factor XIa, catalytic domain of, complex with ecotin mutants 87928-05-0DP, Ecotin, mutant forms, complex with factor XIa
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PREP (Preparation)
(atomic resolution crystallog. structures of blood coagulation factor XIa catalytic domain in complex with ecotin mutants)

L24 ANSWER 2 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:21511 HCAPLUS Full-text
DOCUMENT NUMBER: 142:235379
TITLE: Domain V of β2-Glycoprotein I Binds Factor XI/XIa and Is Cleaved at Lys317-Thr318
AUTHOR(S): Shi, Tong; Giannakopoulos, Bill; Iverson, G. Michael; Cockerill, Keith A.; Linnik, Matthew D.; Krilis, Steven A.
CORPORATE SOURCE: Department of Medicine, Department of Immunology, Allergy & Infectious Diseases, St. George Hospital, University of New South Wales, Sydney, NSW 2217, Australia
SOURCE: Journal of Biological Chemistry (2005), 280(2), 907-912
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB The fifth domain (DV) of β2-glycoprotein I (β2GPI) is important for binding a number of ligands including phospholipids and factor XI (FXI). β2GPI is proteolytically cleaved in DV by plasmin but not by thrombin, VIIa, tissue plasminogen activator, or uPA. Following proteolytic cleavage of DV by plasmin, β2GPI retains binding to FXI but not to phospholipids. Native β2GPI, but not cleaved β2GPI, inhibits activation of FXI by thrombin and factor XIIa, attenuating a pos. feedback mechanism for addnl. thrombin generation. In this report, we have defined the FXI/FXIa binding site on β2GPI using site-directed mutagenesis. We show that the pos. charged residues Lys284, Lys286, and Lys287 in DV are essential for the interaction of β2GPI with FXI/FXIa. We also demonstrate that FXIa proteolytically cleaves β2GPI at Lys317-Thr318 in DV. Thus, FXIa cleavage of β2GPI in vivo during thrombus formation may accelerate FXI activation by decreasing the inhibitory effect of β2GPI.
IT 9013-55-2, Blood-coagulation factor XI 37203-61-5, Blood-coagulation factor XIa
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(domain V of β2-glycoprotein I binds factor XI/XIa and is cleaved at Lys317-Thr318)

L24 ANSWER 3 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:1033547 HCAPLUS Full-text
DOCUMENT NUMBER: 142:19250
TITLE: Crystal structure of coagulation factor XIa-inhibitor complexes yield a pharmacophore structure useful for the design of compounds for treatment of thrombosis
INVENTOR(S): Abdel-Meguid, Sherin S.; Babine, Robert E.; Deng, Hongfeng; Jin, Lei; Lin, Jian; Magee, Scott R.;

Meyers, Harold V.; Pandey, Pramod; Rynkiewicz, Michael J.; Weaver, David T.
PATENT ASSIGNEE(S): Suntory Pharmaceutical Research Laboratories Llc, USA
SOURCE: PCT Int. Appl., 925 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004103270	A2	20041202	WO 2004-US10349	20040402
WO 2004103270	A3	20050512		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005143317	A1	20050630	US 2004-817248	20040402
PRIORITY APPLN. INFO.:			US 2003-459910P	P 20030402

OTHER SOURCE(S): MARPAT 142:19250

TI Crystal structure of coagulation factor XIa-inhibitor complexes yield a pharmacophore structure useful for the design of compounds for treatment of thrombosis

AB The present invention provides compds. that inhibit blood coagulation factor XIa and methods of preventing or treating undesired thrombosis by administering a compound of the invention to a mammal. To facilitate the identification and/or design of high affinity inhibitors for factor XIa, several three-dimensional structures of the human factor XIa catalytic domain (XIcat) bound to a ligand were determined by x-ray diffraction crystallog. A series of amino acid substitution mutants that alter the ability of recombinant human factor XI to be glycosylated in the host and to improve crystallization are also provided. These structures are used to homol. model the structure of other candidate inhibitors with XIcat. In addition, the methods described for the crystallization and structural determination of complexes of XIcat with a ligand are used to exptl. determine the structure of other ligands bound to XIcat. This structural information is used to identify functional groups within a ligand that can be modified to increase the affinity and selectivity of the ligand for factor XIa or to identify functional groups within the ligand that can be modified to increase the bioavailability of the ligand without adversely affecting its affinity for factor XIa. In addition to providing compds. designed based on the structure of XIcat, the present invention includes a class of peptidomimetics and non-peptides that inhibit the activity of factor XIa, and thus useful for treating or preventing diseases for which inhibition of factor XIa is desirable.

ST coagulation factor XIa ligand crystal structure; pharmacophore coagulation factor XIa anticoagulant design; conformation coagulation factor XIa ligand pharmacophore

IT Proteins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(SBP (sex steroid-binding protein), linker-bound to factor XIa inhibitor; crystal structure of coagulation factor XIa-inhibitor complexes yield a pharmacophore structure useful for the design of compds. for treatment of thrombosis)

IT Enzyme functional sites
(active; crystal structure of coagulation factor XIa-inhibitor complexes yield a pharmacophore structure useful for the design of compds. for treatment of thrombosis)

IT Heart, disease
(angina pectoris, unstable, treatment of; crystal structure of coagulation factor XIa-inhibitor complexes yield a pharmacophore structure useful for the design of compds. for treatment of thrombosis)

IT Antiarteriosclerotics
(antiatherosclerotics, treatment of; crystal structure of coagulation factor XIa-inhibitor complexes yield a pharmacophore structure useful for the design of compds. for treatment of thrombosis)

IT Artery
(cerebral, disease, thrombosis, treatment of; crystal structure of coagulation factor XIa-inhibitor complexes yield a pharmacophore structure useful for the design of compds. for treatment of thrombosis)

IT Thrombosis
(coronary arterial, treatment of; crystal structure of coagulation factor XIa-inhibitor complexes yield a pharmacophore structure useful for the design of compds. for treatment of thrombosis)

IT Artery
Vein
(coronary, thromboembolism, treatment of; crystal structure of coagulation factor XIa-inhibitor complexes yield a pharmacophore structure useful for the design of compds. for treatment of thrombosis)

IT Artery, disease
(coronary, thrombosis, treatment of; crystal structure of coagulation factor XIa-inhibitor complexes yield a pharmacophore structure useful for the design of compds. for treatment of thrombosis)

IT Conformation
Drug design
Human
Mus musculus
Oryctolagus cuniculus
Peptidomimetics
Pharmacophores
Rattus norvegicus
(crystal structure of coagulation factor XIa-inhibitor complexes yield a pharmacophore structure useful for the design of compds. for treatment of thrombosis)

IT Polyoxyalkylenes, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(crystal structure of coagulation factor XIa-inhibitor complexes yield a pharmacophore structure useful for the design of compds. for treatment of thrombosis)

IT Artery, disease
Kidney, disease
Lung, disease
(embolism, treatment of; crystal structure of coagulation factor XIa-inhibitor complexes yield a pharmacophore structure useful for the design of compds. for treatment of thrombosis)

IT Heart, disease
Heart, disease
(infarction, treatment of; crystal structure of coagulation factor XIa-inhibitor complexes yield a pharmacophore structure useful for the design of compds. for treatment of thrombosis)

IT Erythrocyte
Erythrocyte
Lymphocyte
Platelet (blood)
(linker-bound to factor XIa inhibitor; crystal structure of coagulation factor XIa-inhibitor complexes yield a pharmacophore structure useful for the design of compds. for treatment of thrombosis)

IT Antibodies and Immunoglobulins
Ferritins
Transcortins
Transferrins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(linker-bound to factor XIa inhibitor; crystal structure of coagulation factor XIa-inhibitor complexes yield a pharmacophore structure useful for the design of compds. for treatment of thrombosis)

IT Protein sequences
(of human blood-coagulation factor XIa mutants; crystal structure of coagulation factor XIa-inhibitor complexes yield a pharmacophore structure useful for the design of compds. for treatment of thrombosis)

IT Crystal structure
(of human coagulation factor XIa-inhibitor complexes)

IT Artery, disease
(peripheral, occlusion, treatment of; crystal structure of coagulation factor XIa-inhibitor complexes yield a pharmacophore structure useful for the design of compds. for treatment of thrombosis)

IT Embolism
(pulmonary, treatment of; crystal structure of coagulation factor XIa-inhibitor complexes yield a pharmacophore structure useful for the design of compds. for treatment of thrombosis)

IT Albumins, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(serum, linker-bound to factor XIa inhibitor; crystal structure of coagulation factor XIa-inhibitor complexes yield a pharmacophore structure useful for the design of compds. for treatment of thrombosis)

IT Brain, disease
Brain, disease
(stroke, treatment of; crystal structure of coagulation factor XIa-inhibitor complexes yield a pharmacophore structure useful for the design of compds. for treatment of thrombosis)

IT Ischemia
(sudden death, treatment of; crystal structure of coagulation factor XIa-inhibitor complexes yield a pharmacophore structure useful for the design of compds. for treatment of thrombosis)

IT Embolism
Heart
(thromboembolism, treatment of; crystal structure of coagulation factor XIa-inhibitor complexes yield a pharmacophore structure useful for the design of compds. for treatment of thrombosis)

IT Proteins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(thyroxine-binding, linker-bound to factor XIa inhibitor; crystal structure of coagulation factor XIa-inhibitor complexes yield a pharmacophore structure useful for the design of compds. for treatment of thrombosis)

IT Heart
(toxicity, thromboembolism, treatment of; crystal structure of coagulation factor XIa-inhibitor complexes yield a pharmacophore structure useful for the design of compds. for treatment of thrombosis)

IT Anti-ischemic agents
Anticoagulants
Atherosclerosis
(treatment of; crystal structure of coagulation factor XIa-inhibitor complexes yield a pharmacophore structure useful for the design of compds. for treatment of thrombosis)

IT Thrombosis
(venous, treatment of; crystal structure of coagulation factor XIa-inhibitor complexes yield a pharmacophore structure useful for the design of compds. for treatment of thrombosis)

IT Macroglobulins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(α2-, linker-bound to factor XIa inhibitor; crystal structure of coagulation factor XIa-inhibitor complexes yield a pharmacophore structure useful for the design of compds. for treatment of thrombosis)

IT 796962-73-7 796962-74-8 796962-75-9D, ligand complexes 796962-76-0 796962-77-1 796962-78-2 796962-79-3 796962-80-6 796962-81-7 796962-82-8D, ligand complexes 796962-83-9 796962-84-0 796962-85-1 796962-86-2 796962-87-3 800415-12-7D, ligand complexes 800415-13-8D, ligand complexes 800415-14-9D, ligand complexes
RL: BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(amino acid sequence; crystal structure of coagulation factor XIa-inhibitor complexes yield a pharmacophore structure useful for the design of compds. for treatment of thrombosis)

IT 618-39-3D, Benzamidine, coagulation factor XI catalytic domain complexes 9013-55-2D, Blood-coagulation factor XI, ligand complexes 37203-61-5D, Blood-coagulation factor XIa, ligand complexes 87928-05-0D, Ecotin, coagulation factor XI catalytic domain complexes
RL: BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(crystal structure of coagulation factor XIa-inhibitor complexes yield a pharmacophore structure useful for the design of compds. for treatment of thrombosis)

IT 776305-43-2P 798555-01-8P 798555-02-9P 798555-03-0P 798555-04-1P 798555-05-2P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(crystal structure of coagulation factor XIa-inhibitor complexes yield a pharmacophore structure useful for the design of compds. for treatment of thrombosis)

IT 70-11-1, 2-Bromo-1-phenylethanone 100-46-9, Benzyl amine, reactions 141-90-2, 2-Thiouracil 5292-43-3, tert-Butyl bromoacetate 5538-51-2, O-Acetylsalicyloyl chloride 5751-20-2, 2-Methylsulfanyl-3H-pyrimidin-4-one 6306-52-1, Valine methyl ester hydrochloride 52927-22-7, 6-Hydroxynaphthalene-2-carbonitrile 61008-98-8, (R)-m-Chloromandelic acid 68635-22-3, 6-Cyano-naphthalene-2-carbonyl chloride 102185-38-6 132131-24-9, 2-Amino-5-iodobenzonitrile 167678-46-8, 2-Methyl-3-acetyloxybenzoic chloride 776306-22-0
RL: RCT (Reactant); RACT (Reactant or reagent)
(crystal structure of coagulation factor XIa-inhibitor complexes yield a pharmacophore structure useful for the design of compds. for treatment of thrombosis)

IT 81560-03-4P, 5-Bromo-2-methylsulfanyl-3H-pyrimidin-4-one 142801-55-6P 201006-25-9P 776305-75-0P 776305-76-1P 776306-08-2P 776306-09-3P 776306-12-8P, 6-Cyano-2-benzylamidonaphthalene 776306-23-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(crystal structure of coagulation factor XIa-inhibitor complexes yield a pharmacophore structure useful for the design of

compds. for treatment of thrombosis)

IT 201541-51-7P 294865-55-7P 308276-66-6P 776305-05-6P 776305-06-7P
776305-07-8P 776305-09-0P 776305-10-3P 776305-11-4P 776305-12-5P
776305-13-6P 776305-14-7P 776305-15-8P 776305-17-0P 776305-18-1P
776305-19-2P 776305-20-5P 776305-21-6P 776305-23-8P 776305-24-9P
776305-25-0P 776305-26-1P 776305-27-2P 776305-28-3P 776305-29-4P
776305-30-7P 776305-31-8P 776305-32-9P 776305-33-0P 776305-34-1P
776305-35-2P 776305-36-3P 776305-37-4P 776305-38-5P 776305-39-6P
776305-40-9P 776305-41-0P 776305-42-1P 776305-44-3P 776305-45-4P
776305-46-5P 776305-47-6P 776305-48-7P 776305-50-1P 776305-52-3P
776305-53-4P 776305-54-5P 776305-55-6P 776305-56-7P 776305-57-8P
776305-58-9P 776305-59-0P 776305-60-3P 776305-61-4P 776305-62-5P
776305-63-6P 776305-64-7P 776305-66-9P 776305-69-2P 776305-70-5P
776305-71-6P 776305-73-8P 776305-74-9P 776305-77-2P 776305-78-3P
776305-80-7P 776305-81-8P 776305-82-9P 776305-84-1P 776305-85-2P
776305-86-3P 776305-87-4P 776305-89-6P 776305-90-9P 776305-91-0P
776305-92-1P 776305-93-2P 776305-94-3P 776305-95-4P 776305-96-5P
776305-98-7P 776305-99-8P 776306-00-4P 776306-01-5P 776306-02-6P
776306-03-7P 776306-04-8P 776306-06-0P 776306-13-9P 776306-15-1P
776306-16-2P 776306-17-3P 776306-18-4P 776306-19-5P 776306-20-8P
776306-21-9P 776306-24-2P 776306-25-3P 776306-26-4P 776306-27-5P
776306-28-6P 776306-30-0P 776306-31-1P 776306-32-2P 776306-33-3P
776306-34-4P 776306-35-5P 776306-36-6P 776306-37-7P 776306-38-8P
776306-39-9P 776306-41-3P 776306-43-5P 776306-44-6P 776306-45-7P
776306-85-5P 798554-83-3P 798554-84-4P 798554-85-5P 798554-86-6P
798554-87-7P 798554-88-8P 798554-89-9P 798554-90-2P 798554-91-3P
798554-92-4P 798554-95-7P 798554-96-8P 798554-97-9P 798554-98-0P
798554-99-1P 798555-00-7P
RL: SPN (Synthetic preparation); PREP (Preparation)
(crystal structure of coagulation factor XIa-inhibitor complexes yield a pharmacophore structure useful for the design of compds. for treatment of thrombosis)

IT 25322-68-3, Polyethylene glycol
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(linker for attachment to blood component; crystal structure of coagulation factor XIa-inhibitor complexes yield a pharmacophore structure useful for the design of compds. for treatment of thrombosis)

IT 800415-15-0D, ligand complexes
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(nucleotide sequence; crystal structure of coagulation factor XIa-inhibitor complexes yield a pharmacophore structure useful for the design of compds. for treatment of thrombosis)

IT 800924-46-3 800924-47-4 800924-48-5 800924-49-6
RL: PRP (Properties)
(unclaimed nucleotide sequence; crystal structure of coagulation factor XIa-inhibitor complexes yield a pharmacophore structure useful for the design of compds. for treatment of thrombosis)

L24 ANSWER 4 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:962591 HCAPLUS Full-text
DOCUMENT NUMBER: 142:21433
TITLE: Severe factor XI deficiency caused by a Gly555 to Glu mutation (factor XI-Glu555): a cross-reactive material positive variant defective in factor IX activation
AUTHOR(S): Zivelin, A.; Ogawa, T.; Bulvik, S.; Landau, M.; Toomey, J. R.; Lane, J.; Seligsohn, U.; Gailani, D.
CORPORATE SOURCE: Amalia Biron Research Institute of Thrombosis and Hemostasis, Chaim Sheba Medical Center, Tel Hashomer and Sackler School of Medicine, Israel
SOURCE: Journal of Thrombosis and Haemostasis (2004), 2(10), 1782-1789
CODEN: JTHOA5; ISSN: 1538-7933
PUBLISHER: Blackwell Publishing Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Severe factor XI deficiency caused by a Gly555 to Glu mutation (factor XI-Glu555): a cross-reactive material positive variant defective in factor IX activation

AB During normal hemostasis, the coagulation protease factor (F)XIa activates FIX. Hereditary deficiency of the FXIa precursor, FXI, is usually associated with reduced FXI protein in plasma, and circulating dysfunctional FXI variants are rare. We identified a patient with < 1% normal plasma FXI activity and normal levels of FXI antigen, who is homozygous for a FXI Gly555 to Glu substitution. Gly555 is two amino acids N-terminal to the protease active site serine residue, and is highly conserved among serine proteases. Recombinant FXI-Glu555 is activated normally by FXIIa and thrombin, and FXIa-Glu555 binds activated factor IX similarly to wild type FXIa (FXIaWT). When compared with FXIaWT, FXIa-Glu555 activates factor IX at a greatly reduced rate (.apprx.400-fold), and is resistant to inhibition by antithrombin. Interestingly, FXIaWT and FXIa-Glu555 cleave the small tripeptide substrate S-2366 with comparable kcats. Modeling indicates that the side chain of Glu555 significantly alters the electrostatic charge around the active site, and would sterically interfere with the interaction between the FXIa S2' site and the P2' residues on factor IX and antithrombin. FXI-Glu555 is the first reported example of a naturally occurring FXI variant with a significant defect in FIX activation.

IT Blood coagulation
(disorder; severe factor XI deficiency caused by Gly555 to Glu mutation (factor XI-Glu555) in relation to factor IX activation)

IT Gene, animal
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(factor XI; severe factor XI deficiency caused by Gly555 to Glu mutation (factor XI-Glu555) in relation to factor IX activation)

IT Gene, animal
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(factor XIa; severe factor XI deficiency caused by Gly555 to Glu mutation (factor XI-Glu555) in relation to factor IX activation)

IT Blood plasma
Human
Molecular association
Mutation
Thrombus
(severe factor XI deficiency caused by Gly555 to Glu mutation (factor XI-Glu555) in relation to factor IX activation)

IT 56-40-6, Glycine, biological studies 9000-94-6, Antithrombin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(severe factor XI deficiency caused by Gly555 to Glu mutation (factor XI-Glu555) in relation to factor IX activation)

IT 9001-28-9, Factor IX 9013-55-2, Blood-coagulation factor XI 37203-61-5, Factor XIa 37316-87-3, Factor IXa
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(severe factor XI deficiency caused by Gly555 to Glu mutation (factor XI-Glu555) in relation to factor IX activation)

L24 ANSWER 5 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:878270 HCAPLUS Full-text
DOCUMENT NUMBER: 141:360682
TITLE: Blood coagulation factor XI inhibitors and methods for treatment of thrombosis
INVENTOR(S): Abdel-Meguid, Sherin S.; Babine, Robert E.; Deng, Hongfeng; Jin, Lei; Lin, Jian; Magee, Scott R.; Meyers, Harold V.; Pandey, Pramod; Rynkiewicz, Michael J.; Weaver, David T.
PATENT ASSIGNEE(S): Suntory Pharmaceutical Research Laboratories, LLC, USA
SOURCE: PCT Int. Appl., 251 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004089297	A2	20041021	WO 2004-US10300	20040402

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005143317	A1	20050630	US 2004-817248	20040402
PRIORITY APPLN. INFO.:			US 2003-459910P	P 20030402

OTHER SOURCE(S): MARPAT 141:360682

IT Blood
(factor XI mutations enhancing lifetime in; blood coagulation factor XI inhibitors and methods for treatment of thrombosis)

IT Solubility
(factor XI mutations enhancing; blood coagulation factor XI inhibitors and methods for treatment of thrombosis)

IT Crystal structure
(of human factor XI complexed with inhibitors; blood coagulation factor XI inhibitors and methods for treatment of thrombosis)

IT 9013-55-2, Blood-coagulation factor XI 37203-61-5, Blood-coagulation factor XIa
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(blood coagulation factor XI inhibitors and methods for treatment of thrombosis)

IT 618-39-3D, Benzamidine, complex with factor XI catalytic domain 87928-05-0D, Ecotin, complex with factor XI catalytic domain
RL: PRP (Properties)
(crystal structure of; blood coagulation factor XI inhibitors and methods for treatment of thrombosis)

L24 ANSWER 6 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:746670 HCAPLUS Full-text
DOCUMENT NUMBER: 142:32893
TITLE: Expression, purification, biochemical and pharmacological characterization of a recombinant aprotinin variant
AUTHOR(S): Apeler, Heiner; Peters, Joerg; Schroeder, Werner; Schneider, Karl-Heinz; Lemm, Georg; Hinz, Volker; Rossouw, Gawie J.; Dembowsky, Klaus
CORPORATE SOURCE: Pharma, Bayer HealthCare AG, Wuppertal, Germany
SOURCE: Arzneimittel Forschung (2004), 54(8), 483-497
CODEN: ARZNAD; ISSN: 0004-4172
PUBLISHER: Editio Cantor Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB Aprotinin (CAS 9087-70-1) is known as a potent inhibitor of serine proteases such as trypsin, plasmin, tissue and plasma kallikrein. In this study, an aprotinin variant was designed by means of rationale mutagenesis that differs from aprotinin by two amino acids in the active site and by seven amino acids in the backbone. The recombinant protein is expressed in a secretory yeast system enabling large scale production A purification procedure was developed to yield high amts. of pure and correctly processed aprotinin variant. The changes in the active site of the aprotinin variant increase the potency towards inhibition of plasma kallikrein whereas the inhibition of plasmin is only marginally reduced. The net charge of the mol. is reduced from the basic (IP 10.5) to the neutral range (IP 5.6). The recombinant aprotinin variant shows a decrease of immunogenicity in several models. No cross-reactivity with human and rabbit antibodies directed against aprotinin was observed both in in vivo and ex vivo studies. In addition, the variant is more potent in a rat brain edema model of acute subdural hematoma compared to aprotinin.

IT 9000-81-1, Acetylcholinesterase 9001-01-8, Urinary kallikrein 9001-90-5, Plasmin 9002-04-4, Thrombin 9002-05-5, Factor Xa 9002-07-7, Trypsin 9004-07-3, Chymotrypsin 9039-53-6, Urokinase 37203-61-5, Factor XIa 42617-41-4, Protein Ca 56645-49-9, Cathepsin G 80295-34-7, Complement C1r 80295-35-8, Complement C1s 97501-93-4, Tryptase 105857-23-6, TPA 111691-85-1, Blood-coagulation factor XIIaβ (human light chain) 410538-33-9, Plasmakallikrein
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(expression, purification, biochem. and pharmacol. characterization of recombinant aprotinin variant)

L24 ANSWER 7 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:597384 HCAPLUS Full-text
DOCUMENT NUMBER: 139:257153
TITLE: The Functional Integrity of the Serpin Domain of C1-inhibitor Depends on the Unique N-terminal Domain, as Revealed by a Pathological Mutant
AUTHOR(S): Bos, Ineke G. A.; Lubbers, Yvonne T. P.; Roem, Dorina; Abrahams, Jan Pieter; Hack, C. Erik; Eldering, Eric
CORPORATE SOURCE: Academic Medical Center, and Landsteiner Laboratory, Sanquin Research at CLB, Department of Immunopathology, University of Amsterdam, Amsterdam, 1066 CX, Neth.
SOURCE: Journal of Biological Chemistry (2003), 278(32), 29463-29470
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

REFERENCE COUNT: 65 THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI The Functional Integrity of the Serpin Domain of C1-inhibitor Depends on the Unique N-terminal Domain, as Revealed by a Pathological Mutant

AB C1-inhibitor (C1-Inh) is a serine protease inhibitor (serpin) with a unique, non-conserved N-terminal domain of unknown function. Genetic deficiency of C1-Inh causes hereditary angioedema. A novel type of mutation (Δ3) in exon 3 of the C1-Inh gene, resulting in deletion of Asp62-Thr116 in this unique domain, was encountered in a hereditary angioedema pedigree. Because the domain is supposedly not essential for inhibitory activity, the unexpected loss-of-function of this deletion mutant was further investigated. The Δ3 mutant and three addnl. mutants starting at Pro76, Gly98, and Ser115, lacking increasing parts of the N-terminal domain, were produced recombinantly. C1-Inh76 and C1-Inh98 retained normal conformation and interaction kinetics with target proteases. In contrast, C1-Inh115 and Δ3, which both lack the connection between the serpin and the non-serpin domain via two disulfide bridges, were completely non-functional because of a complex-like and multimeric conformation, as demonstrated by several criteria. The Δ3 mutant also circulated in multimeric form in plasma from affected family members. The C1-Inh mutant reported here is unique in that deletion of an entire amino acid stretch from a domain not shared by other serpins leads to a loss-of-function. The deletion in the unique N- terminal domain results in a "multimerization phenotype" of C1-Inh, because of diminished stability of the central β-sheet. This phenotype, as well as the location of the disulfide bridges between the serpin and the non-serpin domain of C1-Inh, suggests that the function of the N-terminal region may be similar to one of the effects of heparin in antithrombin III, maintenance of the metastable serpin conformation.

IT Gene
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(C1-Inh; cysteine-containing region of N-terminal domain of C1-inhibitor stabilizes serpin domain by tethering central β-sheet via disulfide bridges)

IT Protein motifs
(N-terminal domain; cysteine-containing region of N-terminal domain of C1-inhibitor stabilizes serpin domain by tethering central β-sheet via disulfide bridges)

IT Blood
Conformational transition
Disulfide group
Human
β-Sheet
(cysteine-containing region of N-terminal domain of C1-inhibitor stabilizes serpin domain by tethering central β-sheet via disulfide bridges)

IT Conformation
(protein; cysteine-containing region of N-terminal domain of C1-inhibitor stabilizes serpin domain by tethering central β-sheet via disulfide bridges)

IT 56-40-6, Glycine, biological studies 56-45-1, L-Serine, biological studies 147-85-3, L-Proline, biological studies 37203-61-5, Factor XIa 37203-62-6, Factor XIIa 410538-33-9, Plasma Kallikrein
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(cysteine-containing region of N-terminal domain of C1-inhibitor stabilizes serpin domain by tethering central β-sheet via disulfide bridges)

IT 80295-38-1, C1 Inhibitor
RL: BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); PRP (Properties); PYP (Physical process); BIOL (Biological study); PROC (Process)
(cysteine-containing region of N-terminal domain of C1-inhibitor stabilizes serpin domain by tethering central β-sheet via disulfide bridges)

L24 ANSWER 8 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:910975 HCAPLUS Full-text
DOCUMENT NUMBER: 138:199168
TITLE: Unusual Proteolytic Activation of Pro-hepatocyte Growth Factor by Plasma Kallikrein and Coagulation Factor XIa
AUTHOR(S): Peek, Mark; Moran, Paul; Mendoza, Nerissa; Wickramasinghe, Dineli; Kirchhofer, Daniel
CORPORATE SOURCE: Department of Physiology, Genentech Inc., South San Francisco, CA, 94080, USA
SOURCE: Journal of Biological Chemistry (2002), 277(49), 47804-47809
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB Hepatocyte growth factor (HGF), the ligand for the receptor tyrosine kinase c-Met, is composed of an α-chain containing four Kringle domains (K1-K4) and a serine protease domain-like β-chain. Receptor activation by HGF is contingent upon prior proteolytic conversion of the secreted inactive single chain form (pro-HGF) into the biol. active two chain form by a single cleavage at the Arg494-Val495 bond. By screening a panel of serine proteases we identified two new HGF activators, plasma kallikrein and coagulation factor XIa (FXIa). The concns. of kallikrein and FXIa to cleave 50% (EC50) of 125I-labeled pro-HGF during a 4-h period were 10 and 17 nm. Unlike other known activators, both FXIa and kallikrein processed pro-HGF by cleavage at two sites. Using N-terminal sequencing they were identified as the normal cleavage site Arg494-Val495 and the novel site Arg424-His425 located in the K4 domain of the α-chain. The identity of this unusual second cleavage site was firmly established by use of the double mutant HGF(R424A/R494E), which was completely resistant to cleavage by kallikrein and FXIa. Expts. with another mutant form, HGF(Arg494 Glu), indicated that cleavage at the K4 site was independent of a prior cleavage at the primary, kinetically preferred Arg494-Val495 site. The cleavage at the K4 site had no obvious consequences on HGF function, because it was fully capable of phosphorylating the c-Met receptor of A549 cells. This may be explained by the disulfide bond network in K4, which holds the cleaved α-chain together. In conclusion, the ability of plasma kallikrein and FXIa to activate pro-HGF in vitro raises the possibility that mediators of inflammation and blood coagulation may also regulate processes that involve the HGF/c-Met pathway, such as tissue repair and angiogenesis.

IT 71-00-1, L-Histidine, biological studies 74-79-3, L-Arginine, biological studies 37203-61-5, Coagulation factor XIa 410538-33-9, Plasma kallikrein
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Pro-HGF unusual proteolytic activation by plasma kallikrein and coagulation factor XIa and arginine-424-histidine-425 cleavage site in)

L24 ANSWER 9 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:721635 HCAPLUS Full-text
DOCUMENT NUMBER: 138:120373
TITLE: The N-terminal Epidermal Growth Factor-like Domain of Coagulation Factor IX. Probing its functions in the activation of factor IX and factor X with a monoclonal antibody
AUTHOR(S): Persson, Kristina E. M.; Villoutreix, Bruno O.; Thamlitz, Ann-Marie; Knobe, Karin E.; Stenflo, Johan
CORPORATE SOURCE: Dep. Clin. Chem., Lund Univ., Univ. Hosp. Malmo, Malmo, S-205 02, Swed.
SOURCE: Journal of Biological Chemistry (2002), 277(38), 35616-35624
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI The N-terminal Epidermal Growth Factor-like Domain of Coagulation Factor IX. Probing its functions in the activation of factor IX and factor X with a monoclonal antibody

AB The absence or reduced activity of coagulation factor IX (FIX) causes the severe bleeding disorder hemophilia B. FIX contains an N-terminal Gla domain followed by two epidermal growth factor-like (EGF) domains and a serine protease domain. In this study, the epitope of monoclonal antibody AW, which is directed against the C-terminal part of the first EGF domain in human FIX, was defined, and the antibody was used to study interactions between the EGF domain of FIX and other coagulation proteins. Antibody AW completely blocks activation of FIX by activated factor XI, but activation by activated factor FVII-tissue factor is inhibited only slightly. The antibody also causes a marginal reduction in the apparent kcat for factor X both in the presence and absence of activated factor VIII. Based on these results, the authors produced a preliminary model of the structure of the activated factor IX-activated factor VIII-AW complex on the surface of phospholipid. The model suggests that in the Xase complex, EGF1 of activated factor IX is not involved in direct binding to activated factor VIII. Studies of the interaction of antibody AW with a mutated FIX mol. (R94D) also suggest that the Glu78-Arg94 salt bridge is not important for maintaining the structure of FIX.

IT Protein motifs
(EGF-like domain; N-terminal epidermal growth factor-like domain of coagulation factor IX in activation of factor IX and factor X with monoclonal antibody against first EGF domain in human FIX)

IT Blood coagulation
Human
(N-terminal epidermal growth factor-like domain of coagulation factor IX in activation of factor IX and factor X with monoclonal antibody against first EGF domain in human FIX)

IT Epitopes
(mapping, mAb AW; N-terminal epidermal growth factor-like domain of coagulation factor IX in activation of factor IX and factor X with monoclonal antibody against first EGF domain in human FIX)

IT Antibodies and Immunoglobulins
RL: BSU (Biological study, unclassified); BUU (Biological use, unclassified); PRP (Properties); BIOL (Biological study); USES (Uses)
(monoclonal, AW Fab fragment, complexes with FIXa and VIIIa; N-terminal epidermal growth factor-like domain of coagulation factor IX in activation of factor IX and factor X with monoclonal antibody against first EGF domain in human FIX)

IT Molecular modeling
(of FIXa-FVIIIa-mAb AW complex; N-terminal epidermal growth factor-like domain of coagulation factor IX in activation of factor IX and factor X with monoclonal antibody against first EGF domain in human FIX)

IT 9035-58-9, Blood-coagulation factor III 37203-61-5, Factor XIa 65312-43-8, Blood coagulation factor VIIa
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(FIX activation by; N-terminal epidermal growth factor-like domain of coagulation factor IX in activation of factor IX and factor X with monoclonal antibody against first EGF domain in human FIX)

IT 9001-29-0, Blood coagulation factor X 113189-77-8, Xase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(N-terminal epidermal growth factor-like domain of coagulation factor IX in activation of factor IX and factor X with monoclonal antibody against first EGF domain in human FIX)

IT 9001-28-9, Blood coagulation factor IX 37316-87-3D, Blood coagulation factor IXa, complexes with VIIIa and mAb AW Fab fragment 72175-66-7D, Blood coagulation factor VIIIa, complexes with FIXa and mAb AW Fab fragment
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(N-terminal epidermal growth factor-like domain of coagulation factor IX in activation of factor IX and factor X with monoclonal antibody against first EGF domain in human FIX)

L24 ANSWER 10 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:742276 HCAPLUS Full-text
DOCUMENT NUMBER: 133:292886
TITLE: Ecotin variants as inhibitors or activators of serine proteinases
INVENTOR(S): Craik, Charles S.; Fletterick, Robert J.; Lundblad, Roger L.; Schwarz, Hans P.
PATENT ASSIGNEE(S): Regents of the University of California, USA
SOURCE: PCT Int. Appl., 97 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000061782	A1	20001019	WO 2000-US9773	20000412

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CA 2369027	AA	20001019	CA 2000-2369027	20000412
EP 1173602	A1	20020123	EP 2000-922111	20000412

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

PRIORITY APPLN. INFO.: US 1999-289830 A 19990412
WO 2000-US9773 W 20000412
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB This invention provides a class of binding proteins that specifically bind to and modulate (e.g. enhance) the activity of polypeptides having a chymotrypsin

fold (e.g. serine proteases). The binding proteins are based on the structure of ecotin. It was discovered that modification of the N- or C-terminus and/or randomization of one or more of loops 50s, 60s, 80s or 100s will provide an ecotin variant library from which can be selected binding mols. (e.g. protease modulators) specific to virtually any serine protease. Depending on the ecotin variant and the target serine protease, the modulator can act as a serine protease inhibitor or as a serine protease activator. Specific agonists (enhancers) of Factor IXa are disclosed.

IT Mutagenesis
(site-directed; ecotin variants as inhibitors or activators of serine proteinases)

IT 9001-01-8, Kallikrein 9001-90-5, Plasmin 9002-04-4, Blood-coagulation factor IIa 9002-05-5, Blood-coagulation factor Xa 9002-07-7, Trypsin 9004-06-2, Elastase 9004-07-3, Chymotrypsin 9014-74-8, Enterokinase 9039-53-6, Urokinase plasminogen activator 9068-57-9, Acrosin 37203-61-5, Blood-coagulation factor XIa 37203-62-6, Blood-coagulation factor XIIa 37213-56-2, Complement factor D 37259-58-8, Serine proteinase 37316-87-3, Blood-coagulation factor IXa 56626-15-4, Complement C3 convertase 56645-49-9, Cathepsin G 65312-43-8, Blood-coagulation factor VIIa 80295-62-1, Complement factor B 80295-69-8, Complement C1r 80295-70-1, Complement C1s 97501-92-3, Chymase 97501-93-4, Tryptase 139639-23-9, Tissue-type plasminogen activator
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(ecotin variants as inhibitors or activators of serine proteinases)

L24 ANSWER 11 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:742142 HCAPLUS Full-text
DOCUMENT NUMBER: 133:292885
TITLE: Ecotin variants as inhibitors or activators of serine proteinases
INVENTOR(S): Craik, Charles S.; Fletterick, Robert J.
PATENT ASSIGNEE(S): Regents of the University of California, USA
SOURCE: PCT Int. Appl., 118 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000061634	A2	20001019	WO 2000-US9790	20000412
WO 2000061634	A3	20010308		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-290513 A 19990412

AB This invention provides a class of binding proteins that specifically bind to and modulate (e.g. enhance) the activity of polypeptides having a chymotrypsin fold (e.g. serine proteases). The binding proteins are based on the structure of ecotin. It was discovered that modification of the N- or C-terminus and/or randomization of one or more of loops 50s, 60s, 80s or 100s will provide an ecotin variant library from which can be selected binding mols. (e.g. protease modulators) specific to virtually any serine protease. Depending on the ecotin variant and the target serine protease, the modulator can act as a serine protease inhibitor or as a serine protease activator. Specific agonists (enhancers) of Factor IXa are disclosed.

IT Mutagenesis
(site-directed; ecotin variants as inhibitors or activators of serine proteinases)

IT 9001-01-8, Kallikrein 9001-90-5, Plasmin 9002-04-4, Blood-coagulation factor IIa 9002-05-5, Blood-coagulation factor Xa 9002-07-7, Trypsin 9004-06-2, Elastase 9004-07-3, Chymotrypsin 9014-74-8, Enterokinase 9039-53-6, Urokinase plasminogen activator 9039-53-6, Urokinase 9068-57-9, Acrosin 37203-61-5, Blood-coagulation factor XIa 37203-62-6, Blood-coagulation factor XIIa 37213-56-2, Complement factor D 37259-58-8, Serine proteinase 37316-87-3, Blood-coagulation factor IXa 56626-15-4, Complement C3 convertase 56645-49-9, Cathepsin G 65312-43-8, Blood-coagulation factor VIIa 80295-62-1, Complement factor B 80295-69-8, Complement C1r 80295-70-1, Complement C1s 97162-88-4, 3C Proteinase 97501-92-3, Chymase 97501-93-4, Tryptase 139639-23-9, Tissue-type plasminogen activator
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(ecotin variants as inhibitors or activators of serine proteinases)

L24 ANSWER 12 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:2200 HCAPLUS Full-text
DOCUMENT NUMBER: 132:133998
TITLE: Identification of amino acids in the factor XI apple 3 domain required for activation of factor IX
AUTHOR(S): Sun, Mao-Fu; Zhao, Mingming; Gailani, David
CORPORATE SOURCE: Departments of Pathology and Medicine, Vanderbilt University, Nashville, TN, 37232-6305, USA
SOURCE: Journal of Biological Chemistry (1999), 274(51), 36373-36378
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB Activated coagulation factor XI (factor XIa) proteolytically cleaves its substrate, factor IX, in an interaction requiring the factor XI A3 domain. To identify key amino acids involved in factor IX activation, recombinant factor XIa proteins containing alanine substitutions for wild-type sequence were expressed in 293 fibroblasts and tested in a plasma clotting assay. Substitutions for Ile183-Val191 and Ser195-Ile197 at the N terminus and for Ser258-Ser264 at the C terminus of the A3 domain markedly decreased factor XI coagulant activity. The plasma protease prekallikrein is structurally homologous to factor XI, but activated factor IX poorly. A chimeric factor XIa mol. with the A3 domain replaced with A3 from prekallikrein (FXI/PKA3) activated factor IX with a Km 35-fold greater than that of wild-type factor XI. FXI/PKA3 was used as a template for a series of proteins in which prekallikrein A3 sequence was replaced with factor XI sequence to restore factor IX activation. Clotting and kinetics studies using these chimeras confirmed the results obtained with alanine mutants. Amino acids between Ile183 and Val191 are necessary for proper factor IX activation, but addnl. sequence between Ser195 and Ile197 or between Phe260 and Ser265 is required for complete restoration of activation.

ST coagulation factor XIa apple 3 domain mutagenesis; factor IX activation coagulation factor XIa

IT 37203-61-5, Blood coagulation factor XIa
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(identification of amino acids in factor XI apple 3 domain required for activation of factor IX)

L24 ANSWER 13 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:619334 HCAPLUS Full-text
DOCUMENT NUMBER: 131:331929
TITLE: Interspecies loop grafting in the protease domain of human protein C yielding enhanced catalytic and anticoagulant activity
AUTHOR(S): Shen, Lei; Villoutreix, Bruno O.; Dahlback, Bjorn
CORPORATE SOURCE: Wallenberg Lab., Dep. Clinical Chemistry, Hospital Malmo, Lund Univ., Malmo, S-20502, Swed.
SOURCE: Thrombosis and Haemostasis (1999), 82(3), 1078-1087
CODEN: THHADQ; ISSN: 0340-6245
PUBLISHER: F. K. Schattauer Verlagsgesellschaft mbH
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB Human anticoagulant activated protein C (hAPC) is less potent than the bovine APC (bAPC) mol. and the aims were to elucidate the mol. background for this difference and to create an APC with enhanced anticoagulant activity. In the protease domain of human protein C (hPC), the loop 148 (GWGYHSSREKEAKRN) is 4 residues longer than the corresponding loop in bovine APC (GWGY RDETKRN). To investigate whether this caused the species difference, the loop in hPC was replaced by the shorter bovine loop, whereas the longer human loop was introduced in bovine protein C. The mutation in hAPC yielded enhanced catalytic activity against chromogenic (4-fold) as well as natural (factors Va and VIIIa) substrates and 2-3-fold increased anticoagulant activity. The opposite effects were obtained with the bovine mutant. As compared to wild-type hAPC, the mutant hAPC was inhibited slightly faster by the protein C inhibitor, whereas the inhibition by α1-antitrypsin was unaffected by the mutation. A computer model of bAPC was developed to analyze further these data. The results demonstrate enhanced catalytic efficiency to result from mutagenesis in the loop 148 and show that APC mutant with increased anticoagulant activity can be created.

IT Anticoagulants
Protein motifs
(APC mutant in protease domain with increased anticoagulant activity)

IT Structure-activity relationship
(anticoagulant; APC mutant in protease domain with increased anticoagulant activity)

IT Molecular modeling
(conformation of APC mutant in loop 148 with increased anticoagulant activity)

IT Enzyme kinetics
Michaelis constant
(kinetics of APC mutant in protease domain with increased anticoagulant activity)

IT Conformation
(protein; conformation of APC mutant in protease domain with increased anticoagulant activity)

IT 9001-92-7, Protease 250133-87-0 250133-88-1
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(APC mutant in protease domain with increased anticoagulant activity)

IT 65522-14-7, Blood coagulation factor Va
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(APC mutant in protease domain with increased anticoagulant activity)

IT 60202-16-6, Protein C
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(chimeric, bovine and human; APC mutant in protease domain with increased anticoagulant activity)

IT 72175-66-7, Blood coagulation factor VIIIa
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(complex with FIXa; APC mutant in protease domain with increased anticoagulant activity)

IT 37203-61-5, Blood coagulation factor XIa
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(complex with FVIIIa; APC mutant in protease domain with increased anticoagulant activity)

IT 62354-65-8, s 2238 72194-57-1, s 2366 108963-69-5
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(substrate specificity of APC mutant in protease domain with increased anticoagulant activity)

L24 ANSWER 14 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:614172 HCAPLUS Full-text
DOCUMENT NUMBER: 131:225815
TITLE: Screening for blood coagulation defects using metal ions
INVENTOR(S): Rosen, Bert Steffen; Hall, Christina Maria Yvonne
PATENT ASSIGNEE(S): Chromogenix AB, Swed.
SOURCE: PCT Int. Appl., 67 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9947699	A1	19990923	WO 1999-EP1599	19990311

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 947585	A1	19991006	EP 1998-105043	19980319
EP 947585	B1	20010725		

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
AT 203567	E	20010815	AT 1998-105043	19980319

PT 947585	T	20011130	PT 1998-105043	19980319
ES 2162361	T3	20011216	ES 1998-105043	19980319
CA 2334935	AA	19990923	CA 1999-2334935	19990311
AU 9930339	A1	19991011	AU 1999-30339	19990311
AU 758831	B2	20030403		
NZ 506747	A	20030328	NZ 1999-506747	19990311
US 6395501	B1	20020528	US 1999-273413	19990319
GR 3036865	T3	20020131	GR 2001-401728	20011011
US 2002115127	A1	20020822	US 2002-50441	20020116
US 6730490	B2	20040504		
US 2003199014	A1	20031023	US 2002-331731	20021230
US 6800450	B2	20041005		
US 2004235078	A1	20041125	US 2004-856108	20040528
PRIORITY APPLN. INFO.:			EP 1998-105043	A 19980319
			WO 1999-EP1599	W 19990311
			US 1999-273413	A1 19990319
			US 2002-50441	A1 20020116

REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT 9001-24-5D, Blood-coagulation factor V, mutants
RL: ANT (Analyte); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)
(screening for blood coagulation defects using metal ions)

IT 476-66-4, Ellagic acid 7631-86-9, Silica, biological studies 7773-01-5, Manganese chloride 7785-87-7, Manganese sulfate 7786-30-3, Magnesium chloride, biological studies 10043-52-4, Calcium chloride, biological studies 10377-60-3, Magnesium nitrate 14127-61-8, Calcium ion, biological studies 14701-22-5, Ni2+, biological studies 15158-11-9, Cu2+, biological studies 16397-91-4, Mn2+, biological studies 17493-86-6, Cuprous ion, biological studies 22537-22-0, Mg2+, biological studies 22537-39-9, Sr2+, biological studies 23713-49-7, Zn2+, biological studies 37203-61-5, Blood-coagulation Factor XIa 37203-62-6, Blood-coagulation Factor XIIa 37316-87-3, Blood-coagulation Factor IXa 69670-93-5, Cephotest 110617-83-9, Protac C
RL: ARG (Analytical reagent use); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(screening for blood coagulation defects using metal ions)

L24 ANSWER 15 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1999:437705 HCAPLUS Full-text
DOCUMENT NUMBER: 131:226567
TITLE: An Arg/Ser substitution in the second epidermal growth factor-like module of factor IX introduces an O-linked carbohydrate and markedly impairs activation by factor XIa and factor VIIa/tissue factor and catalytic efficiency of factor IXa
AUTHOR(S): Hertzberg, Mark S.; Facey, Sandra L.; Hogg, Philip J.
CORPORATE SOURCE: Department of Haematology, Westmead Hospital and University of Sydney, Sydney, Australia
SOURCE: Blood (1999), 94(1), 156-163
CODEN: BLOOAW; ISSN: 0006-4971
PUBLISHER: W. B. Saunders Co.
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB Factor IXR94S is a naturally occurring hemophilia B defect, which results from an Arg 94 to Ser mutation in the second epidermal growth factor (EGF)-like module of factor IX. Recombinant factor IXR94S was activated by factor XIa/calcium with an ≈50-fold reduced rate and by factor VIIa/tissue factor/phospholipid/calcium with an ≈20-fold reduced rate compared with wild-type factor IX. The apparent mol. mass of the light chain of factor IXaR94S was ≈6 kDa higher than that of plasma or wild-type factor IX, which was not corrected by N-glycosidase F digestion. This result indicated the presence of addnl. O-linked carbohydrate in the mutant light chain, probably at new Ser 94. The initial rate of activation of factor X by factor IXaR94S in the presence of polylysine was 7% ± 1% of the initial rate of activation of factor X by plasma factor IXa, and the kc/Km for activation of factor X by factor IXaR94S/factor VIIIa/phospholipid/calcium was 4% ± 1% of the kc/Km for activation of factor X by plasma factor IXa/factor VIIIa/phospholipid/calcium. The reduced efficiency of activation of factor X by factor IXaR94S in the tenase enzyme complex was due to a 58-fold ± 12-fold decrease in kcat with little effect on Km. In conclusion, the R94S mutation had introduced an O-linked carbohydrate, which markedly impaired both activation by factor XIa and turnover of factor X in the tenase enzyme complex.

ST arginine serine substitution factor IX carbohydrate hemophilia B coagulation; EGF factor motif mutation XIa VIIa IXa activation

IT Mutation
(point; Arg/Ser substitution in second epidermal growth factor-like module of factor IX introduces O-linked carbohydrate and markedly impairs activation by factor XIa and factor VIIa/tissue factor and catalytic efficiency of factor IXa)

IT 9035-58-9, Tissue factor (blood-coagulation) 37203-61-5, Blood coagulation factor XIa 65312-43-8, Blood coagulation factor VIIa 72175-66-7, Blood coagulation factor VIIIa
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(Arg/Ser substitution in second epidermal growth factor-like module of factor IX introduces O-linked carbohydrate and markedly impairs activation by factor XIa and factor VIIa/tissue factor and catalytic efficiency of factor IXa)

L24 ANSWER 16 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1998:798721 HCAPLUS Full-text
DOCUMENT NUMBER: 130:151492
TITLE: Inhibition of serine proteases by reactive site mutants of protein C inhibitor (plasminogen activator inhibitor-3)
AUTHOR(S): Elisen, M. G. L. M.; Bouma, B. N.; Church, F. C.; Meijers, J. C. M.
CORPORATE SOURCE: Department of Haematology, University Hospital, Utrecht, 3508 GA, Neth.
SOURCE: Fibrinolysis & Proteolysis (1998), 12(5), 283-291
CODEN: FBPRFP; ISSN: 1369-0191
PUBLISHER: Churchill Livingstone
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Inhibition of serine proteases by reactive site mutants of protein C inhibitor (plasminogen activator inhibitor-3)

AB Protein C inhibitor (PCI), also known as plasminogen activator inhibitor-3, is a heparin-dependent serine protease inhibitor. Heparin and other sulfated polysaccharides act as template, thereby increasing the rate of inhibition by PCI. PCI can inhibit various serine proteases in blood coagulation, fibrinolysis and reproduction However, its physiol. target enzyme is still unknown. Reactive site mutants of PCI were used to elucidate its target specificity, which may provide clues towards its function in vivo. We have studied the importance of the region P3-P3' of PCI in reactivity towards acrosin, kallikrein, factor XIa and urokinase. The kinetic anal. was performed using both pseudo first-order kinetics and slow-binding kinetics. The results demonstrated the importance of the P3-P3' region and in particular the P2 and P3 residues of PCI in protease recognition. The data showed the preference of a hydrophobic residue at P2 for the inhibition of kallikrein and acrosin, whereas alanine at P2 benefits the inhibition of urokinase inhibition. In addition to the preference for a hydrophobic P2 residue for serpin reactivity towards kallikrein and acrosin, it was also shown that a pos. charged residue at P3 also benefits serpin reactivity towards these proteases. The results further support the general idea that reactive site residues are important for the specificity of the serpin, but that these are not solely responsible for serpin specificity. We observed that heparin affected the specific activity of acrosin but not of kallikrein. In addition, acrosin inhibition by PCI was strongly enhanced by heparin, whereas PCI reactivity towards kallikrein was unaffected by this glycosaminoglycan. Since heparin acts as template, the mechanism of stimulation of PCI reactivity by heparin is most likely the result of bringing both protease and PCI in close proximity and not by inducing major changes in the conformation affecting the reactive site loop. Therefore, the binding of PCI to the heparin template affects the orientation of the reactive site towards the active site of the protease and this suggests that the heparin-binding domains of PCI are also determinants in target specificity of PCI.

IT Blood coagulation
(inhibition of serine proteases by reactive site mutants of protein C inhibitor (plasminogen activator inhibitor-3))

IT 9005-49-6, Heparin, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(inhibition of serine proteases by reactive site mutants of protein C inhibitor (plasminogen activator inhibitor-3))

IT 9001-01-8, Kallikrein 9039-53-6, Urokinase 9068-57-9, Acrosin 37203-61-5, Factor XIa 37259-58-8, Serine protease
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(inhibition of serine proteases by reactive site mutants of protein C inhibitor (plasminogen activator inhibitor-3))

IT 139691-92-2, Serine protease inhibitor
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(inhibition of serine proteases by reactive site mutants of protein C inhibitor (plasminogen activator inhibitor-3))

IT 139466-48-1, Protein C inhibitor
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(region P3-P3' of; inhibition of serine proteases by reactive site mutants of protein C inhibitor (plasminogen activator inhibitor-3))

L24 ANSWER 17 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1998:763381 HCAPLUS Full-text
DOCUMENT NUMBER: 130:92091
TITLE: Characterization of a heparin binding site on the heavy chain of factor XI
AUTHOR(S): Zhao, Mingming; Abdel-Razek, Tarek; Sun, Mao-Fu; Gailani, David
CORPORATE SOURCE: Department of Pathology and Medicine, Vanderbilt University, Nashville, TN, 37232, USA
SOURCE: Journal of Biological Chemistry (1998), 273(47), 31153-31159
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB The glycosaminoglycan heparin enhances several reactions involving coagulation factor XI (FXI) including activation of FXI by factor XIIa, thrombin, and autoactivation; and inactivation of activated FXI (FXIa) by serine protease inhibitors. We examined the effect of heparin on inhibition of FXIa by the inhibitors C1-inhibitor (C1-INH) and antithrombin III (ATIII). Second order rate consts. for inhibition in the absence of heparin were 1.57 + 103 and 0.91 + 103 M-1 s-1 for C1-INH and ATIII, resp. Therapeutic heparin concns. (0.1-1.0 units/mL) enhanced inhibition by ATIII 20-55-fold compared with 0.1-7.0-fold for C1-INH. For both inhibitors, the effect of heparin over a wide range of concns. (10-1 to 105 units/mL) produced bell-shaped curves, demonstrating that inhibition occurs by a template mechanism requiring both inhibitor and protease to bind to heparin. This implies that FXI/XIa contains structural elements that interact with heparin. Human FXI contains a sequence of amino acids (R250-I-K-K-S-K) in the apple 3 domain of the heavy chain that binds heparin (Ho, D., Badellino, K., Baglia, F., and Walsh, P. (1998) J. Biol. Chemical 273, 16382-16390). To determine the importance of this sequence to heparin-mediated reactions, recombinant FXI mols. with alanine substitutions for basic amino acids were expressed in 293 fibroblasts, and tested in heparin-dependent assays. Inhibition of FXIa by ATIII in the presence of heparin was decreased 4- fold by alanine substitution at Lys253 (A253), with smaller effects noted for mutants A255 and A252. FXI undergoes autoactivation to FXIa in the presence of heparin. The rate of autoactivation was decreased substantially for A253 with modest decreases for A255 and A252. Substituting all four charged residues in the sequence resulted in a profound decrease in autoactivation, significantly greater than for any single substitution. Relative affinity for heparin was tested by determining the concentration of NaCl required to elute FXIa from heparin-Sepharose. Wild type FXIa eluted from the column at 320 mM NaCl, whereas FXIa with multiple substitutions (A252-254 or A250-255) eluted at 230 mM NaCl. All proteins with single substitutions in charged amino acids eluted at intermediate NaCl concns. The data indicate that FXI/XIa must bind to heparin for optimal inhibition by ATIII and for autoactivation. Lys253 is the most important amino acid involved in binding, and Lys255 and Lys252 also have roles in interactions with heparin.

IT 37203-61-5, Blood coagulation factor XIa
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(characterization of a heparin binding site on the heavy chain of factor XI)

L24 ANSWER 18 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1997:621128 HCAPLUS Full-text
DOCUMENT NUMBER: 127:305789
TITLE: Interaction of factor IXa with factor VIIIa. Effects of protease domain Ca2+ binding site, proteolysis in the autolysis loop, phospholipid, and factor X
AUTHOR(S): Mathur, Akash; Zhong, Degang; Sabharwal, Arun K.; Smith, Kenneth J.; Bajaj, S. Paul

CORPORATE SOURCE: Departments of Medicine, Pathology, and Biochemistry, St. Louis University School of Medicine, St. Louis, MO, 63104, USA
SOURCE: Journal of Biological Chemistry (1997), 272(37), 23418-23426
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 58 THERE ARE 58 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB We previously identified a high affinity Ca2+-binding site in the protease domain of factor IXa involving Glu235 (Glu70 in chymotrypsinogen numbering; hereafter, the nos. in brackets refer to the chymotrypsin equivalent) and Glu245[80] as putative ligands. To delineate the function of this Ca2+-binding site, we expressed IXwild type (IXWT), IXE235K, and IXE245V in 293 kidney cells and compared their properties with those of factor IX isolated from normal plasma (IXNP); each protein had the same Mr and γ-carboxyglutamic acid content. Activation of each factor IX protein by factor VIIa·Ca2+·tissue factor was normal as analyzed by sodium dodecyl sulfate gel electrophoresis. The coagulant activity of IXaWT was .apprx.93%, of IXaE235K was .apprx.27%, and of IXaE245V was .apprx.4% compared with that of IXaNP. In contrast, activation by factor XIa·Ca2+ led to proteolysis at Arg318-Ser319[150-151] in the protease domain autolysis loop of IXaE245V with a concomitant loss of coagulant activity; this proteolysis was moderate in IXaE235K and minimal in IXaWT or IXaNP. Interaction of each activated mutant with an active site probe, p-aminobenzamidine, was also examined; the Kd of interaction in the absence and presence (in parentheses) of Ca2+ was: IXaNP or IXaWT 230 μM (78 μM), IXaE235K 150 μM (145 μM), IXaE245V 225 μM (240 μM), and autolysis loop-cleaved IXaE245V 330 μM (350 μM). Next, we evaluated the apparent Kd (Kd,app) of interaction of each activated mutant with factor VIIIa. We first investigated the EC50 of interaction of IXaNP as well as of IXaWT with factor VIIIa in the presence and absence of phospholipid (PL) and varying concns. of factor X. At each factor X concentration and constant factor VIIIa, EC50 was the the free IXaNP or IXaWT concentration that yielded a half-maximal rate of factor Xa generation. EC50 values for IXaNP and IXaWT were similar and are as follows: PL-minus/X-minus (extrapolated), 2.8 μM; PL-minus/X-saturating, 0.25 μM; PL-plus/X-minus, 1.6 nM; and PL-plus/X-saturating, 0.09 nM. Further, Kd,app of binding of active site-blocked factor IXa to factor VIIIa was calculated from its ability to inhibit IXaWT in the Tenase assay. Kd,app values in the absence and presence (in parentheses) of PL were: IXaNP or IXaWT, 0.19 μM (0.07 nM); IXaE235K, 0.68 μM (0.26 nM); IXaE245V, 2.5 μM (1.35 nM); and autolysis loop-cleaved IXaE245V, 15.6 μM (14.3 nM). We conclude that (a) PL increases the apparent affinity of factor IXa for factor VIIIa .apprx.2,000-fold, and the substrate, factor X, increases this affinity .apprx.10-15-fold; (b) the protease domain Ca2+ binding site increases this affinity .apprx.15-fold, and lysine at position 235 only partly substitutes for Ca2+; (c) Ca2+ binding to the protease domain increases the S1 reactivity .apprx.3- fold and prevents proteolysis in the autolysis loop; and (d) proteolysis in the autolysis loop leads to a loss of catalytic efficiency with retention of the S1 binding site and a further .apprx.8-fold reduction in affinity of factor IXa for factor VIIIa.

IT 37203-61-5D, Blood-coagulation factor XIa, calcium complex
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(factor IX activation by; effects of protease domain Ca2+-binding site, proteolysis in autolysis loop, phospholipid, and factor X on interaction of factor IXa with factor VIIIa)

L24 ANSWER 19 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:315550 HCAPLUS Full-text
DOCUMENT NUMBER: 127:62439
TITLE: Modification of the N-terminus of human factor IX by defective propeptide cleavage or acetylation results in a destabilized calcium-induced conformation: effects on phospholipid binding and activation by factor XIa
AUTHOR(S): Wojcik, Emiel G. C.; van den Berg, Marieke; Poort, Swibertus R.; Bertina, Rogier M.
CORPORATE SOURCE: Hemostasis and Thrombosis Research Centre, Dep. of Hematology, University Hospital, Leiden, 2300 RC, Neth.
SOURCE: Biochemical Journal (1997), 323(3), 629-636
CODEN: BIJOAK; ISSN: 0264-6021
PUBLISHER: Portland Press
DOCUMENT TYPE: Journal
LANGUAGE: English

TI Modification of the N-terminus of human factor IX by defective propeptide cleavage or acetylation results in a destabilized calcium-induced conformation: effects on phospholipid binding and activation by factor XIa

AB The propeptide of human coagulation factor IX (FIX) directs the γ-carboxylation of the first 12 glutamic acid residues of the mature protein into γ-carboxyglutamic acid (Gla) residues. The propeptide is normally removed before secretion of FIX into the blood. However, mutation of Arg-4 in the propeptide abolishes propeptide cleavage and results in circulating profactor IX in the blood. Three such genetic variants, factor IX Boxtel (Arg-4→Trp), factor IX Bendorf (Arg-4→Leu) and factor IX Seattle C (Arg-4→Gln), were studied. These variant profactor IX mols. bind normally to anti-FIX:Mg(II) antibodies, which indicates that the mutations do not seriously affect γ-carboxylation. Metal ion titration of the binding of variant profactor IX to conformation-specific antibodies demonstrates that the calcium-induced conformation is destabilized in the variant mols. Also the binding of FIX Boxtel to phospholipids and its activation by factor XIa requires a high (>5 mM) calcium concentration The 3-dimensional structure of the Gla domain of FIX in the presence of calcium indicates that the acylation of the N-terminus, rather than the presence of the propeptide, was responsible for the destabilization of the calcium-induced conformation. In order to confirm this, the α-amino group of Tyr1 of FIX was acetylated. This chemical modified FIX showed a similar destabilization of the calcium-induced conformation of variant profactor IX. The data imply that the N- terminus of FIX plays an important role in stabilizing the calcium-induced conformation of the Gla domain of FIX. This conformation is important for the binding to phospholipids as well as for the activation by factor XIa. The results indicate that mutations in FIX that interfere with propeptide cleavage affect the function of the protein mainly by destabilizing the calcium-induced conformation.

IT Phospholipids, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(N-terminal modification of human factor IX by defective propeptide cleavage or acetylation results in a destabilized calcium-induced conformation and effects phospholipid binding and activation by factor XIa)

IT Peptides, properties
RL: PRP (Properties)
(N-terminal propeptides; N-terminal modification of human factor IX by defective propeptide cleavage or acetylation results in a destabilized calcium-induced conformation and effects phospholipid binding and activation by factor XIa)

IT Conformation
(protein; N-terminal modification of human factor IX by defective propeptide cleavage or acetylation results in a destabilized calcium-induced conformation and effects phospholipid binding and activation by factor XIa)

IT 7440-70-2, Calcium, biological studies 37203-61-5, Blood-coagulation factor XIa
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(N-terminal modification of human factor IX by defective propeptide cleavage or acetylation results in a destabilized calcium-induced conformation and effects phospholipid binding and activation by factor XIa)

IT 9001-28-9, Blood-coagulation factor IX 191490-54-7, Pro-blood-coagulation factor IX Bendorf 191490-55-8, Pro-blood-coagulation factor IX Boxtel 191490-56-9, Pro-blood-coagulation factor IX Seattle C
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(N-terminal modification of human factor IX by defective propeptide cleavage or acetylation results in a destabilized calcium-induced conformation and effects phospholipid binding and activation by factor XIa)

L24 ANSWER 20 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:898665 HCAPLUS Full-text
DOCUMENT NUMBER: 123:309290
TITLE: Potent and selective Kunitz domain inhibitors of plasma kallikrein designed by phage display
AUTHOR(S): Dennis, Mark S.; Herzka, Andrea; Lazarus, Robert A.
CORPORATE SOURCE: Dep. Protein Eng., Genentech, Inc., South San Francisco, CA, 94080, USA
SOURCE: Journal of Biological Chemistry (1995), 270(43), 25411-17
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Phage displaying APPI Kunitz domain libraries have been used to design potent and selective active site inhibitors of human plasma kallikrein, a serine protease that plays an important role in both inflammation and coagulation. Selected clones from two Kunitz domain libraries randomized at or near the binding loop (positions 11-13, 15-19, and 34) were sequenced following five rounds of selection on immobilized plasma kallikrein. Invariant preferences for Arg at position 15 and His at position 18 were found, whereas His, Ala, Ala, and Pro were highly preferred residues at positions 13, 16, 17, and 19, resp. At position 11 Pro, Asp, and Glu were favored, while hydrophobic residues were preferred at position 34. Selected variants, purified by trypsin affinity chromatog. and reverse phase high performance liquid chromatog., potently inhibited plasma kallikrein, with apparent equilibrium dissociation consts. (Ki*) ranging from .apprx.75 to 300 pM. From sequence and activity data, consensus mutants were constructed by site directed mutagenesis. One such mutant, KALI-DY, which differed from APPI at 6 key residues (T11D, P13H, M17A, I18H, S19P, and F34Y), inhibited plasma kallikrein with a Ki* = 15 pM, representing an increase in binding affinity of more than 10,000-fold compared to APPI. Similar to APPI, the variants also inhibited Factor XIa with high affinity, with Ki* values ranging from .apprx.0.3 to 15 nM; KALI-DY inhibited Factor XIa with a Ki* = 8.2 nM. KALI-DY did not inhibit plasmin, thrombin, Factor Xa, Factor XIIa, activated protein C, or tissue factor·Factor VIIa. Consistent with the protease specificity profile, KALI-DY did not prolong the clotting time in a prothrombin time assay, but did prolong the clotting time in an activated partial thromboplastin time assay >3.5-fold at 1 μM.

IT 9001-01-8, Kallikrein 37203-61-5, Blood-coagulation factor XIa
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(potent and selective Kunitz domain inhibitors of plasma kallikrein designed by phage display)

L24 ANSWER 21 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:594978 HCAPLUS Full-text
DOCUMENT NUMBER: 121:194978
TITLE: Kunitz domain inhibitors of tissue factor-factor VIIa. I. Potent inhibitors selected from libraries by phage display
AUTHOR(S): Dennis, Mark S.; Lazarus, Robert A.
CORPORATE SOURCE: Department of Protein Engineering, Genentech, Inc., South San Francisco, CA, 94080, USA
SOURCE: Journal of Biological Chemistry (1994), 269(35), 22129-36
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Potent active-site inhibitors of human tissue factor-Factor VIIa (TF·FVIIa) have been selected from Alzheimer's amyloid β-protein precursor inhibitor (APPI) Kunitz domain libraries displayed on phage. Eight randomized positions on the extended primary binding loop (P5 through P4') and positions 34 and 39 were examined in three sep. libraries. Libraries contained from 3.2+105 to 3.2+106 potential variants resulting from replacing ≤5 positions with all 20 amino acids. Following 4 rounds of selection against FVIIa associated with immobilized tissue factor (TF), 12 clones from each library were sequenced. Variants were purified by trypsin affinity chromatog. and reverse-phase high performance liquid chromatog., and characterized for their ability to inhibit TF·FVIIa chromogenic activity. Measured apparent equilibrium dissociation consts. (Ki*) ranged from about 10 to 500 nM. From sequence and activity data, an overall consensus sequence, TF7I-C, was constructed by site-directed mutagenesis. TF7I-C differed from APPI at 4 key residues, T11P, M17L, S19L, and G39Y, and inhibited TF·FVIIa with a Ki* = 1.9 nM, which represented an increase in binding affinity of more than 150-fold compared to APPI. At 40 μM, TF7I-C prolonged the clotting times 3.5-fold at 7 μM in an activated partial thromboplastin time assay. Prolongation of the activated partial thromboplastin time correlates with potent inhibition of FXIa (Ki* = 0.8 nM) and plasma kallikrein (Ki* = 1.2 nM). TF7I-C also inhibited plasmin (Ki* = 40 nM) and FXa (Ki* = 55 nM), but not activated protein C, thrombin, or FXIIa (Ki* > 10 μM each).

IT 9001-01-8, Kallikrein 9001-90-5, Plasmin 9002-05-5, Blood coagulation factor Xa 37203-61-5, Blood coagulation factor XIa
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(inhibitors; Kunitz domain inhibitors of human tissue factor-factor VIIa selected from libraries by phage display)

L24 ANSWER 22 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:320547 HCAPLUS Full-text
DOCUMENT NUMBER: 120:320547
TITLE: The Arg-4 mutant factor IX Strasbourg 2

shows a delayed activation by factor XIa
AUTHOR(S): De la Salle, C.; Charmantier, J. L.; Ravanat, C.; Ohlmann, P.; Hartmann, M. L.; Schuhler, S.; Bischoff, R.; Ebel, C.; Roecklin, D.; et al.
CORPORATE SOURCE: Cent. Reg. Transfus. Sanguine, Strasbourg, F-67085, Fr.
SOURCE: Nouvelle Revue Francaise d'Hematologie (1993), 35(5), 473-80
CODEN: NRFHA4; ISSN: 0029-4810
DOCUMENT TYPE: Journal
LANGUAGE: English
TI The Arg-4 mutant factor IX Strasbourg 2 shows a delayed activation by factor XIa
AB The authors have characterized at the DNA and protein levels a mutant factor IX, factor IX Strasbourg 2, which is responsible for a severe form (<0.01 U/mL) of hemophilia B. Factor IX Strasbourg 2 has a higher mol. weight than normal factor IX. A mutation G→A at position 6365 of the gene was demonstrated by DNA sequencing and confirmed by restriction mapping which showed absence of a Hae III site. This leads to the substitution of glutamine for arginine at position -4 of the propeptide. Factor IX Strasbourg 2 was purified from plasma by DEAE Sepharose chromatog. and immunoaffinity and relative to normal factor IX, binding of calcium to the mutant protein was clearly reduced in calcium lactate agarose gel. Quantification of γ-carboxyglutamic acid residues gave about 50% carboxylation as compared to normal factor IX. Microsequencing of the NH2-terminal part of factor IX Strasbourg 2 confirmed the attachment of the propeptide and the mutation Arg→Gln. Activation of factor IX Strasbourg 2 by purified factor XIa was found to be retarded as compared to normal factor IX, but after activation the mutant factor IXa was able to activate factor X. Strasbourg 2 circulates with the attached propeptide and shows reduced γ-carboxylation and delayed activation by factor XIa but a normal capacity to activate factor X after total cleavage by factor XIa.
IT Hemophilia
(B, blood coagulation factor IX Strasbourg 2 mutant mediation of blood coagulation factor XIa in, in human)
IT 37203-61-5, Blood coagulation factor XIa
RL: BIOL (Biological study)
(blood coagulation factor IX Strasbourg 2 mutant mediation of, in human hemophilia B)
IT 155215-88-6, Blood-coagulation factor IX Strasbourg 2
RL: BIOL (Biological study)
(mutation in, blood coagulation factor XIa mediation by, in human hemophilia B)

L24 ANSWER 23 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:294986 HCAPLUS Full-text
DOCUMENT NUMBER: 120:294986
TITLE: First epidermal growth factor-like domain of human blood coagulation factor IX is required for its activation by factor VIIa/tissue factor but not by factor XIa
AUTHOR(S): Zhong, Degang; Smith, Kenneth J.; Birktoft, Jens J.; Bajaj, S. Paul
CORPORATE SOURCE: Sch. Med., Saint Louis Univ., St. Louis, MO, 63104, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1994), 91(9), 3574-8
CODEN: PNASA6; ISSN: 0027-8424
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Factor IX consists of a γ-carboxyglutamic acid-rich domain followed by two epidermal growth factor (EGF)-like domains and the C- terminal protease domain. To delineate the function of EGF1 domain in factor IX, the authors constructed three mutants: an EGF1 domain-deleted mutant (IXΔEGF1), a point mutant (IXQ50P) with a Gln-50 → Pro change, and a replacement mutant (IXPCEGF1) in which the EGF1 domain of factor IX was replaced by that of protein C. These mutants and wild-type (WT) factor IX (IXWT) were expressed in 293 kidney cells by using pRc/CMV vector. The purified proteins had the same γ-carboxyglutamic acid content as the normal plasma factor IX (IXNP) and were activated normally by factor XIa-Ca2+. In contrast, IXΔEGF1 could not be activated by factor VIIa-tissue factor-Ca2+, and the activation of IXPCEGF1 in this system was markedly slow; however, IXQ50P was activated at a normal rate. In addnl. studies, both IXWT and IXΔEGF1 were rapidly converted to their resp. IXα forms by factor Xa-phospholipid-Ca2+. Since this reaction has an absolute requirement for phospholipid, it indicates that the mutants under study are not impaired in their interactions with phospholipid. Relative coagulant activities of factor XIa-activated proteins were IXNP, 100%; IXWT, 75-85%; IXΔEGF1, ≤1%; IXPCEGF1, ≤2%; and IXQ50P, 6-10%. The authors conclude that the EGF1 domain of factor IX is required for its activation by factor VIIa-tissue factor and that the Gln-50 residue is not critical for this activation. Further, the EGF1 domain of factor IX is not essential for phospholipid binding and for its activation by factor XIa. In addition, the low coagulant activities of the activated mutants indicate that the EGF1 domain is also important in factor X activation by factor IXa-factor VIIIa-Ca2+-phospholipid complex.
IT 37203-61-5, Blood-coagulation factor xia
RL: BIOL (Biological study)
(blood-coagulation factor IX activation by, EGF-like domain in relation to)

L24 ANSWER 24 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:425771 HCAPLUS Full-text
DOCUMENT NUMBER: 119:25771
TITLE: Mutations in the catalytic domain of factor IX that are related to the subclass hemophilia Bm
AUTHOR(S): Hamaguchi, Nobuko; Roberts, Harold; Stafford, Darrel W.
CORPORATE SOURCE: Thromb. Hemostasis Cent., Univ. North Carolina, Chapel Hill, NC, 27599, USA
SOURCE: Biochemistry (1993), 32(25), 6324-9
CODEN: BICHAW; ISSN: 0006-2960
DOCUMENT TYPE: Journal
LANGUAGE: English
TI Mutations in the catalytic domain of factor IX that are related to the subclass hemophilia Bm
AB Hemophilia Bm, a variant of hemophilia B, results in a marked increase in the ox brain prothrombin time. Mutations known to cause hemophilia Bm occur at residue 180, 181, or 182 near the amino terminus of the heavy chain and at residue 311, 364, 368, 390, 396, or 397 near the activation site of factor IX. In this study factor IX residues 181, 182, and 390 were replaced in sep. expts. by site-directed mutagenesis. Valine 181 was replaced by isoleucine or alanine, and valine 182 was replaced by alanine or glycine. Alanine 390 was replaced by valine or aspartic acid. Recombinant factor IXs were expressed in human kidney 293 cells and purified by absorption and elution from a conformational specific monoclonal antibody column. The results show that factor IX Bm is a function not only of the position of the mutated amino acid but also of the particular amino acid substituted. For example, when valine 181 or 182 was replaced by small hydrophobic amino acids (alanine and glycine), factor IXs were found to have decreased clotting activity. Unlike the naturally occurring mutations (Val181->Phe181 or Val182->Leu182), however, the small amino acid replacements did not result in prolonged ox brain prothrombin times. Surprisingly, the Ala390->Asp390 exchange did not affect clotting activity or binding to the macromol. inhibitor antithrombin III. The Ala390->Val390 exchange resulted in loss of both clotting activity and binding to antithrombin III. Apparently, residue 390 is not directly involved in binding to antithrombin III. Furthermore, residue 390 probably does not make significant intermol. interactions. It is likely those factor IX Bm variants with mutations at 181, 182, or 390 are defective in the conformational change required for activation, which normally occurs upon cleavage between residues 180 and 181.
ST coagulation factor IX mutation hemophilia Bm
IT 9001-29-0, Blood-coagulation factor X
RL: BIOL (Biological study)
(mutant blood coagulation factor IXa activation of, hemophilia Bm in relation to)
IT 37203-61-5, Blood-coagulation factor XIa
RL: BIOL (Biological study)
(mutant blood-coagulation factor IX activation by, hemophilia Bm in relation to)
IT 3858-83-1, p-Aminobenzamidine 9000-94-6, Antithrombin III
RL: BIOL (Biological study)
(mutant blood-coagulation factor IX binding to, hemophilia Bm in relation to)

L24 ANSWER 25 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1991:576699 HCAPLUS Full-text
DOCUMENT NUMBER: 115:176699
TITLE: Recombinant preparation of serpin-resistant serine proteinases of the chymotrypsin superfamily
INVENTOR(S): Sambrook, Joseph F.; Madison, Edwin L.; Goldsmith, Elizabeth J.; Gething, Maryjane H.; Gerard, Robert D.
PATENT ASSIGNEE(S): University of Texas System, USA
SOURCE: PCT Int. Appl., 76 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 9010649	A1	19900920	WO 1990-US947		19900301
W: AU, BB, BG, BR, CA, FI, HU, JP, KP, KR, LK, MC, MG, MW, NO, RO, SD, SU					
RW: AT, BE, BF, BJ, CF, CG, CH, CM, DE, DK, ES, FR, GA, GB, IT, LU, ML, MR, NL, SE, SN, TD, TG					
US 5550042	A	19960827	US 1989-434748		19891113
AU 9052780	A1	19901009	AU 1990-52780		19900301
AU 637791	B2	19930610			
EP 462207	A1	19911227	EP 1990-905081		19900301
EP 462207	B1	20010207			
R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, LU, NL, SE					
JP 04504952	T2	19920903	JP 1990-505024		19900301
JP 2991769	B2	19991220			
AT 199090	E	20010215	AT 1990-905081		19900301
PRIORITY APPLN. INFO.:			US 1989-319212	A	19890306
			US 1989-434748	A	19891113
			WO 1990-US947	A	19900301

AB Analogs of serine proteinase of the chymotrypsin superfamily, e.g. human tissue-type plasminogen activator (t-PA) mutants that are resistant to their cognate inhibitors, are prepared by expression of the mutagenized genes in animal cells. Serine protease inhibitor mutants, e.g. the human plasminogen activator inhibitor (PAI), with higher inhibitory activities are also prepared The t-PA substitution or deletion analogs affecting the catalytic region (amino acids 296-304) were prepared by oligonucleotide-mediated mutagenesis and expression of the genes in COS cells. Some analogs showed greater resistance to PAI-1, e.g. t-PA(R304 → S and t-PA(R304 → E) showed 4- and 25-fold more resistance, resp. Km and Kcat, detd using Des-A-fibrinogen (25 µg/mL) or Lys-plasminogen (0.02-0.16 µM) as substrates, of the mutants were not significantly changed. Preparation of the PAI-1 mutants by similar methods and their characterizationwere also demonstrated.
ST plasminogen activator mutant inhibitor resistance; serine protease mutant inhibitor resistance; chymotrypsin superfamily mutant
IT 9001-01-8DP, Kallikrein, amino acid-substituted analogs 9001-90-5DP, Plasmin, amino acid-substituted analogs 9002-04-4DP, Thrombin, amino acid-substituted analogs 9002-05-5DP, Blood-coagulation factor Xa, amino acid-substituted analogs 9002-07-7DP, Trypsin, amino acid-substituted analogs 9004-06-2DP, Elastase, amino acid-substituted analogs 9068-57-9DP, Acrosin, amino acid-substituted analogs 37203-61-5DP, Blood-coagulation factor XIa, amino acid-substituted analogs 37203-62-6DP, Factor XIIa, amino acid-substituted analogs 37316-87-3DP, Blood-coagulation factor IXa, amino acid-substituted analogs 56645-49-9P, Cathepsin G 65312-43-8DP, Blood-coagulation factor VIIa, amino acid-substituted analogs 80295-70-1DP, amino acid-substituted analogs 97501-92-3DP, Chymase, amino acid-substituted analogs
RL: PREP (Preparation)
(peptide inhibitor-resistant, recombinant preparation of)

L24 ANSWER 26 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1989:405226 HCAPLUS Full-text
DOCUMENT NUMBER: 111:5226
TITLE: Functional consequences of an arginine180 to glutamine mutation in factor IX Hilo
AUTHOR(S): Monroe, Dougald M.; McCord, Dean M.; Huang, Min Ning; High, Katherine A.; Lundblad, Roger L.; Kasper, Carol K.; Roberts, Harold R.
CORPORATE SOURCE: Dep. Med., Univ. North Carolina, Chapel Hill, NC, USA
SOURCE: Blood (1989), 73(6), 1540-4
CODEN: BLOOAW; ISSN: 0006-4971
DOCUMENT TYPE: Journal
LANGUAGE: English
TI Functional consequences of an arginine180 to glutamine mutation in factor IX Hilo
AB Factor IX Hilo is a variant factor IX mol. that has no detectable coagulant activity. The defect in factor IX Hilo arises from a point mutation in the gene such that in the protein Arg180 is converted to a Gln. Activation of factor IX Hilo by factor XIa was monitored using the fluorescent active site probe p-aminobenzamidine. Normal factor IX showed complete activation in one h as determined by measuring the increase in fluorescence when p-aminobenzamidine bound to activated factor IX. Factor IX Hilo showed no increase in fluorescence even after 24 h, indicating that the active site was not exposed. PAGE showed that factor IX Hilo was cleaved to a light chain plus a larger peptide with a mol. weight equivalent to a heavy chain covalently linked to an activation peptide. Amino terminal amino acid sequencing of factor IX Hilo cleaved by factor XIa showed cleavage only at Arg145-Ala146, indicating that the Gln180-Val181 bond was not cleaved and that the active site was thus not exposed. The presence of factor IX Hilo in

patient plasma was responsible for the patient having a very long ox brain prothrombin time characteristic of severe hemophilia Bm. When factor IX Hilo was depleted from patient plasma using an immunoaffinity column, the ox brain prothrombin time decreased to 41 s. When factor IX Hilo was added back to depleted patient plasma, to normal plasma depleted of factor IX by the same affinity column, or to plasma from a CRM- hemophilia B patient, the ox brain prothrombin time was significantly prolonged. Thus, the Arg180 to Gln mutation in factor IX Hilo results in a mol. that cannot be activated by factor XIa. Further, the mutation results in a mol. that interacts with components of the extrinsic pathway to give a prolonged ox brain prothrombin time.

IT 37203-61-5, Blood-coagulation factor XIa
RL: BIOL (Biological study)
(blood-coagulation factor IX Hilo activation by, of human)

L24 ANSWER 27 OF 27 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1986:125615 HCAPLUS Full-text
DOCUMENT NUMBER: 104:125615
TITLE: Alpha-1-antitrypsin-Pittsburgh. A potent inhibitor of human plasma factor XIa, kallikrein, and factor XIIf
AUTHOR(S): Scott, Cheryl F.; Carrell, Robin W.; Glaser, Charles B.; Kueppers, Friedrich; Lewis, Jessica H.; Colman, Robert W.
CORPORATE SOURCE: Health Sci. Cent., Temple Univ., Philadelphia, PA, 19140, USA
SOURCE: Journal of Clinical Investigation (1986), 77(2), 631-4
CODEN: JCINAO; ISSN: 0021-9738
DOCUMENT TYPE: Journal
LANGUAGE: English

AB α1-Antitrypsin-Pittsburgh (AT-P) is a human variant that resulted from a point mutation in the plasma protease inhibitor, AT (358 Met → Arg). This defect in the AT mol. causes it to have greatly diminished anti-elastase activity but markedly increased antithrombin activity. This variant protein also has greatly increased inhibitory activity towards the arginine-specific enzymes of the contact system of plasma proteolysis (Factor XIa, kallikrein, and Factor XIIf), in contrast to normal AT, which has modest to no inhibitory activity towards these enzymes. The 2nd-order-inactivation rate constant (k'') of purified, human Factor XIa by purified AT-P was 5.1 + 105 M-1 s-1 (23°), which is a 7700-fold increase over the k'' for Factor XIa by its major inhibitor, normal purified AT (i.e., 6.6 + 101 M-1 s-1). Human plasma kallikrein, which is poorly inhibited by AT (k'' = 4.2 M-1 s-1), exhibited a k'' for AT-P of 8.9 + 104 M-1 s-1 (a 21,000- fold increase), making it a more efficient inhibitor than either of the naturally occurring major inhibitors of kallikrein (C.hivin.1-inhibitor and α2-macroglobulin). Factor XIIf, which is not inhibited by normal AT, displayed a k'' for AT-P of 2.5 + 104 M-1 s-1. This enhanced inhibitory activity is similar to the effect of AT-P that has been reported for thrombin. In addition to its potential as an anticoagulant, this recently cloned protein may prove to be clin. valuable in the management of septic shock, hereditary angioedema, or other syndromes involving activation of the surface-mediated plasma proteolytic system.

IT Kinetics, enzymic
(of inactivation, of kallikrein and blood-coagulation factors XIa and XIIf of human, mutation in α1-antitrypsin in relation to)

IT 9001-01-8 37203-61-5 75216-42-1
RL: PROC (Process)
(inhibition of, by α1-antitrypsin-Pittsburgh of human, kinetics of)

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L*** DEL    2 S US 2005143317/PN OR US 2003-459910#/AP,PRN

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L2             TRA L1 1- RN :        229 TERMS

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L4         40 SEA PLU=ON  L3 AND FACTOR (1A) XI?
L*** DEL    0 L4 AND S434A
L5         26 SEA PLU=ON  L4 AND 434 (1A) ALAN?
L6         27 SEA PLU=ON  L4 AND 475 (1A) ALAN?
L7         24 SEA PLU=ON  L5 AND L6
L8         20 SEA PLU=ON  L7 AND ((422 OR 437 OR 486 OR 505 OR 509 OR 479 OR
              476) (1A) ALAN? OR 482 (1A) SER?)
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              D SCAN
L11        24 SEA PLU=ON  (L7 OR L8 OR L9 OR L10)

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              D L12 1-2 IBIB ED
              E FACTOR XI/CT
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L14         0 SEA PLU=ON  BLOOD COAG/CT
              E BLOOD COAG/CT
              E ABDEL (1A) MEGUID/AP
              E ABDEL (1A) MEGUID/IN
              E ABDEL MEGUID/IN
              E MEGUID/IN

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              E FACTOR XI/CN

     FILE 'HCAPLUS' ENTERED AT 11:22:46 ON 29 JUL 2005
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     FILE 'REGISTRY' ENTERED AT 11:23:53 ON 29 JUL 2005
L15         3 SEA PLU=ON  ("FACTOR XI (HUMAN PLASMA SUBUNIT MATURE FORM)"/CN
              OR "FACTOR XI (HUMAN PLATELET SUBUNIT MATURE FORM)"/CN OR
              "FACTOR XIA"/CN)

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     FILE 'HCAPLUS' ENTERED AT 11:23:59 ON 29 JUL 2005
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L18        42 SEA PLU=ON  L17 AND MUTA?
L19         3 SEA PLU=ON  L18 AND SULF?
L20         3 SEA PLU=ON  L18 AND CRYST?
L21         5 SEA PLU=ON  L18 AND CHARG?
L22        12 SEA PLU=ON  L18 AND TERMIN?
L23        12 SEA PLU=ON  L18 AND FOLD?
L24        27 SEA PLU=ON  (L19 OR L20 OR L21 OR L22 OR L23)
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              D COST

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FILE HOME

FILE HCAPLUS

FILE COVERS 1907 - 29 Jul 2005 VOL 143 ISS 6
FILE LAST UPDATED: 28 Jul 2005 (20050728/ED)

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FILE REGISTRY
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DICTIONARY FILE UPDATES: 28 JUL 2005 HIGHEST RN 857521-63-2

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* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added,   *
* effective March 20, 2005. A new display format, IDERL, is now     *
* available and contains the CA role and document type information. *
*                                                             *
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Structure search iteration limits have been increased. See HELP SLIMITS for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

FILE STNGUIDE
FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Jul 22, 2005 (20050722/UP).

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